

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Van Beusechem

Examiner: Scott Long

Serial No: 10/501,407

Group Art Unit: 1633

Confirmation No.: 9615

Docket No.: 294-293 PCT/US/RCE

Filing Date: March 25, 2005

Dated: April 4, 2011

For: VIRUSES WITH ENHANCED LYTIC POTENCY

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I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system on April 4, 2011.

Lauren T. Emr

(Printed Name)

Signature: /Lauren T. Emr/

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

**DECLARATION OF FRANK MCCORMICK, PHD, FRS UNDER 37 C.F.R. § 1.132**

I, Frank McCormick, PhD, FRS, declare as follows:

1) I am Director of the Helen Diller Family Comprehensive Cancer Center & Cancer Research Institute of the University of California, San Francisco (UCSF). I was founder and Scientific Director of Onyx Pharmaceuticals and as such have been actively involved in pre-clinical and clinical development of oncolytic adenoviruses, amongst which the ONYX-OIS product which has been tested in various clinical studies. I have been practicing in the field of adenovirus gene therapy for 18 years. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

2) I have read U.S. Patent Application No. 10/501,407 and the related office actions dated July 6, 2010 and December 2, 2010. In particular, I have read the comments from the examiner that claims 26-35 and 38-40 are obvious in view of Curiel et al. (US-6,824,771) and

Xu et al. (Human Gene Therapy 1997; 8:177-185), and that claims 36-37 are obvious over the same references also in view of Lin et al. (Cancer Research 2000; 60:5895-5901). I have also read the response by the applicant thereto filed on November 8, 2010, and the references Curiel et al., Xu et al., and Lin et al. I understand that similar objections have been raised by the examiner based on the combination of Hallenbeck et al (Human Gene Therapy 1999; 10:1721-1733) and Lin et al.; and Fueyo et al. (Oncogene 2000; 19:2-12) and Lin et al. Therefore, I have also read Hallenbeck et al and Fueyo et al.

3) The unexpected discovery that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy was, in my opinion, highly novel and certainly not predictable from available research publications, at the time the instant application was filed. Specifically, it was not predictable from the teachings of Curiel et al., Xu et al., or Lin et al., or from a combination thereof. The Hallenbeck et al. and the Fueyo et al. references resemble the Curiel et al reference in that they address oncolytic viruses, albeit that the specific oncolytic virus is different from the one discussed by Curiel et al.

4) The fact that the oncolytic virus was slightly different is not of particular relevance. As stated above, the finding that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy was, in my opinion, highly novel and certainly not predictable from previous research publications.

5) On the contrary, at the time the instant application was filed, it was expected that restoration of functional p53 would suppress viral replication, as suggested by Hermiston and Kuhn (Cancer Gene Therapy, 2002; 9:1022-1035) and others. This is because p53 is actively degraded during viral replication, and adenoviruses that fail to degrade p53 are defective for replication in normal primary human cells (O'Shea et al., Cancer Cell, 2004; 6:611-623). This view was re-enforced recently by O'Shea and coworkers (Soria et al., Nature 2010; 466: 1076-1081) who showed that adenoviral E4 proteins contribute to inactivation of p53 during infection, in addition to the well-known effect of E1B 55K on p53 degradation. Therefore, restoration of

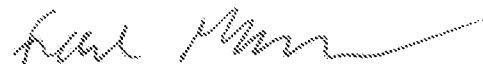
functional p53 would be expected to suppress virus replication rather than enhancing it. A copy of Soria et al. is attached as Exhibit B.

6) Another surprising aspect of the instant application's discovery is that p53 expressed in an adenovirus remains functional at all. Adenoviruses shut down host protein synthesis and synthesis of viral genes expressed from certain early promoters. It was therefore unexpected that p53 could remain functional (documented in van Beusechem et al., *Cancer Research* 2002; 62:6165-6171) and promote expression of downstream genes. The recent work of Soria et al. cited above also underscores the fact that adenoviruses encode multiple mechanisms to eradicate and inactivate p53 during infection: the activity demonstrated by the instant invention was therefore unexpected for several distinct reasons.

7) The idea that direct, forced, expression of p53 in a p53-negative tumor cell promotes growth arrest, or cell death, has been well established for many years. However, this effect is clearly distinct from the novel role of p53 in promoting virus replication, as discovered in the instant application. The importance of the instant invention is based on the presumption that clinical efficacy depends on robust virus replication and infection of multiple tumor cells, rather than direct killing of a single transduced cell by a non-replicating viral vector.

8) For these reasons, I believe that the concepts underlying the instant patent application are novel and were not at all predictable/obvious based on prior publications or disclosures, at the time of the invention.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed:  Dated: 3/19/2011  
Dr. Frank McCormick

# **EXHIBIT A**

University of California, San Francisco

Updated: 1/31/11

## CURRICULUM VITAE

**Name:** Frank McCormick, PhD, FRS, DSc (Hon)

**Position:** Director, UCSF Helen Diller Family Comprehensive Cancer Center  
E. Dixon Heise Distinguished Professor in Oncology  
David A. Wood Distinguished Professor of Tumor Biology and Cancer Research

Associate Dean, School of Medicine

Distinguished Professor in Residence, Department of Microbiology and Immunology  
Distinguished Professor in Residence, Department of Biochemistry and Biophysics

**Address:** UCSF Helen Diller Family Comprehensive Cancer Center  
1450 3rd Street, Room HD-371, UCSF Box 0128  
San Francisco, CA 94158-9001

Voice: 415-502-1710

Fax: 415-502-1712

E-mail: [mccormick@cc.ucsf.edu](mailto:mccormick@cc.ucsf.edu)

www: <http://cancer.ucsf.edu/>

### EDUCATION:

1968-72	University of Birmingham, England, UK	B.Sc.	Biochemistry
1972-75	University of Cambridge, England, UK	Ph.D.	Biochemistry

### LICENSES, CERTIFICATION:

Not Applicable

### PRINCIPAL POSITIONS HELD:

1975-1978	State University of New York at Stony Brook	Fellow	Prof. Seymour S. Cohen
1978-1981	Imperial Cancer Research Fund, London	Fellow	Dr. Alan Smith
1981-1990	Cetus Corporation		Director of Molecular Biology
1990-1991	Cetus Corporation		Vice President, Research
1991-1992	Chiron Corporation		Vice President, Research
1992-1996	Onyx Pharmaceuticals		Founder, Chief Scientific Officer
1997-now	University of California, San Francisco		Director
	Helen Diller Family Comprehensive Cancer Center and Cancer Research Institute		
1997-now	University of California, San Francisco, School of Medicine		Associate Dean
1997-now	University of California, San Francisco, Department of Microbiology and Immunology		Professor

## HONORS AND AWARDS:

1996	Fellow of the Royal Society
2002	Bristol Myers Squibb Unrestricted Cancer Research Grant
2002	AACR – G.H.A. Clowes Memorial Award
2002	Novartis Drew Award in Biomedical Research
2003	University of Chicago, Cancer Research Center, Shubitz Award
2004	Nomination, Alfred P. Sloan, Jr. Prize, General Motors Cancer Research Foundation
2005	Institute of Medicine
2008	Salute to Excellence Award, American Liver Foundation
2008	Honorary Degree, Doctor of Science, University of Birmingham, England, UK
2010	ASCO Science of Oncology Award

## KEYWORDS/AREAS OF INTEREST:

Cancer, virology, Ras, p53, oncogenes, tumor suppressors, breast cancer, neurofibromatosis, protein kinases

## PROFESSIONAL ACTIVITIES:

### PROFESSIONAL ORGANIZATIONS

#### Memberships

1997-now	American Association for Cancer Research
1997-now	American Society for Microbiology
1998-now	American Association for the Advancement of Science
1998-now	American Society of Gene Therapy
2005-now	Institute of Medicine
2008-now	American Society of Clinical Oncology

#### Service to Professional Organizations

1997-2003	ONYX Pharmaceuticals	Scientific Advisory Board
1998-1999	NCI Developmental Therapeutics Program	Scientific Advisory Board
1998-2003	NCI Board of Scientific Counselors	Advisory Committee
1998-2001	ICONIX Pharmaceuticals	Scientific Advisory Board
1998-2004	The Jackson Laboratory Bar Harbor, Maine	Scientific Advisory Board
1998-2007	Friedrich Miescher-Institut	External Advisory Board
2000-now	Van Andel Institute	Scientific Advisory Board
2001-2002	Sagres	Scientific Advisory Board
2001-now	University of Wisconsin Comprehensive Cancer Center	External Advisory Board
2002-2005	American Association of Cancer Research	Board of Directors
2002-2006	Alberta Cancer Board	Advisory Committee on Research
2002-2007	Alliance for Cancer Gene Therapy	Scientific Advisory Council
2003-2006	Association of American Cancer Institutes	Board of Directors
2003-2010	Memorial Sloan-Kettering Cancer Center	Board of Scientific Consultants
2003-now	Exelixis, Inc	Board of Directors
2003-now	NCI Initiative for Chemical Genetics	External Review Committee
2003-2008	Nexgenix Pharmaceuticals, LLC	Scientific Advisory Board
2004-2009	Emory Winship Cancer Institute	External Advisory Board
2004-now	Canary Foundation	Scientific Advisory Board
2005-2007	Friends of Cancer Research	Scientific Advisory Board

2005-2007	UT Southwestern Medical Center, Harold C. Simmons Comprehensive Cancer Center	External Advisory Board
2005-2008	American Association for Cancer Research	Finance Committee
2005-now	Columbia University, New York, Herbert Irving Comprehensive Cancer Center	Scientific Advisory Board
2005-now	Aglaia Biomedical Ventures B.V.	Scientific Advisory Board
2006-2007	Burnham Institute for Medical Research	Scientific Advisory Board
2006-now	Fluidigm Corporation	Scientific Advisory Board
2006-2007	KineMatik Limited	Scientific Advisory Board
2006-2008	MannKind Corporation	Scientific Advisory Board
2006-now	Melanoma Therapeutics Foundation	Board and Scientific Advisory Board
2007-2008	BiPar Sciences	Scientific Advisory Board
2007-now	Daiichi-Sankyo, Ltd.	Scientific Advisory Board
2008-now	TriAct Therapeutics, Inc	Scientific Advisory Board
2008-now	ORCA Therapeutics, Inc	Scientific Advisory Board
2008-now	Dana-Farber/Harvard Cancer Center	External Advisory Board
2008-2010	Arresto Biosciences	Board of Directors
2008-now	Life Sciences Institute	Scientific Advisory Board
2009-now	Van Andel Institute	Faculty Committee Review
2009-now	Dicerna	Scientific Advisory Board
2009-now	Jennerex Biotherapeutics, Inc.	Scientific Advisory Board
2010-now	Aduro BioTech	Board of Directors and Scientific Advisory Board
2010-now	Duke University	Scientific Advisory Board
2010-now	Portola Pharmaceuticals	Translational Advisory Board

#### **Organizing Committees:**

2001	AACR Program Committee 93 <sup>rd</sup> Annual Meeting	Co-Chair
2003	Gordon Research Conference, Molecular Therapeutics of Cancer Queen's College, Oxford, UK	Vice-Chair
2003	AACR, Nominating Committee for the Laboratory Research Awards and Professorship	Member
2004	Gordon Research Conference, Molecular Therapeutics of Cancer Colby Sawyer College, New Hampshire	Chair
2004	AACR, Nominating Committee for the Laboratory Research Awards and Professorship	Member
2004	AACI, Annual Meeting Program Committee	Chair
2005	Keystone Symposium, Molecular Targets for Cancer Therapy	Co-Chair
2005	AACR Award for Lifetime Achievement in Cancer Research Selection Committee	Chair
2006	AACR Major Scientific Symposium: MEK Inhibitors and Target Ras Pathways	Chair
2006	Nature-Centro Nacional de Investigaciones Oncologicas (CNIO) International Conference: Oncogenes and Human Cancer: The Next 25 Years, Scientific Organizing Committee	Member
2007	AACR-Eli Lilly Team Science Award Selection Committee	Chair
2007	AACR-NCI-EORTC Scientific Committee	Member
2007	Netherlands Genomics Initiative: Cancer Genomics Center Workshop Organizing Committee	Member
2010	AACR Program Committee 101st Annual Meeting	Chair
2010	AACR Task Force of Co-development of Investigational Drugs	Chair

2010	AACR Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research	Member
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## **SERVICE TO PROFESSIONAL PUBLICATIONS**

### **Editorial Boards:**

1991-now	Cell Growth and Differentiation
1995-1998	Molecular and Cellular Biology
1996-now	BBA Reviews on Cancer-Elsevier
1998-now	Neoplasia
2001-now	Cancer Cell
2002-2007	Molecular Cancer Research (Senior Editor)
2003-2007	Journal of Molecular Medicine (U.S. Editor-in-Chief)

### **Ad hoc Reviewing:**

1997	Cancer Research, Nature, Oncogene, Science
1998	Cancer Research, Clinical Cancer Research, EMBO, Grant Review for Human Frontier Science Program Organization, Nature Medicine, News & Views, Oncogene, PNAS, Science, Structural Nature
1999	American Heart Association Circulation Research Journal, Biochemistry, Blood Journal, Dutch Cancer Society, FASEB Journal, Human Gene Therapy, Journal of Clinical Investigation, Molecular Microbiology, National Academy of Sciences, Nature, Nature Oncology Research, Science, Tumor Targeting, Nature Medicine
2000	Cancer Research, Cell Biology International, Clinical Cancer Research, Gene and Development, Journal of Clinical Oncology, National Academy of Sciences, Nature Biotechnology, Nature Medicine, PNAS, Science
2001	British Journal of Cancer, Cancer Research, EMBO, Journal of Molecular Biology, Journal of Virology, Nature Cell Biology, Nature Structural Biology, Nature Medicine, Science, Structure, Oncology
2002	Cancer Research, Cell Biochemistry and Biophysics, Journal of Clinical Investigation, Journal of Clinical Oncology, Journal of Virology, Proceedings of the National Academy of Sciences, Nature Biotechnology, Nature Medicine
2003	The Cancer Journal
2007	BMC-series Journal, Oncogene
2008	Oncogene, PNAS

## **INVITED PRESENTATIONS:**

### **INTERNATIONAL:**

2002	Faculty of Medicine, Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, Canada, Robert B. Church Lecturer in Biotechnology 2001
2002	"A Century Colloquium", Imperial Cancer Research Fund, University of Warwick, England, UK.
2003	MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Cambridge, England, UK.
2003	Keystone Symposium on Molecular and Cellular Biology, "Cancer Therapy Based on the p53 Pathway", Banff, Alberta, Canada.
2003	Ontario Regional Cancer Centre, "Oncolytic Viruses as Cancer Therapeutics", Banff, Alberta, Canada.
2003	Max-Planck-Institut für Molekulare Physiologie, Annual Retreat, Ringberg, Bavaria, Germany.



- 2003 Beatson International Cancer Conference, Keynote Speaker, Cell Signaling and Cancer Conference, Cancer Research UK, Glasgow, Scotland, UK.
- 2003 The Institute of Cancer Research, The Royal Marsden Tenth Annual Link Lecture, Royal Cancer Hospital, Surrey and London, England, UK.
- 2003 European Molecular Biology Organization/Federation of European Biochemical Societies, Molecular Mechanisms in Signal Transduction, Spetses, Greece.
- 2003 The 41<sup>st</sup> Annual Meeting of Japan Society of Clinical Oncology, Sapporo, Japan.
- 2003 Alberta Cancer Board Annual Research Meeting, Banff, Alberta, Canada.
- 2004 90<sup>th</sup> Annual Meeting of the Japan Society of Gastroenterology, "The Front Line of Cancer Therapy", Sendai, Japan.
- 2004 Fondation des Treilles, "New Anti-Cancer Approaches Based on our Molecular Understanding of Oncogenesis", Tourtour, France.
- 2004 University of Warwick, Genes and Cancer 2004, 21<sup>st</sup> Meeting, Warwick, England, UK.
- 2004 Canadian Institutes of Health Research, Institute of Genetics and Institute of Cancer Research, Third Annual Investigators Meeting, Jackson Point, Ontario, Canada.
- 2004 Molecular Biology/Signal Transduction Seminar, McMaster University, Hamilton, Ontario, Canada.
- 2005 Biomedical Research Council Distinguished Visitor, Singapore.
- 2005 The 8<sup>th</sup> Annual New England Biolabs Symposium on Molecular and Cellular Biology New England Biolabs, Pickering, Ontario, Canada.
- 2005 Cancer Genomics Center, Genomic Approaches and Molecular Mechanisms in Cancer, Royal Tropical Institute, Amsterdam, The Netherlands.
- 2006 9<sup>th</sup> Cancer Research UK Beatson International Cancer Conference: 24 Years of Ras and Human Cancer, Caledonian University, Glasgow, Scotland, UK.
- 2007 British Columbia Cancer Research Centre, 2007 Richard T. Israels QC Memorial Lecture; Vancouver, British Columbia, Canada.
- 2007 The National Cancer Research Institute Cancer Conference, Birmingham, England, UK.
- 2007 Nature/CNIO (Centro Nacional de Investigaciones) Conference: "Oncogenes and Human Cancer: The Next 25 Years," Madrid, Spain.
- 2007 Cancer Genomics Centre Workshop, "GEFs and GAPs as therapeutic targets." Utrecht, The Netherlands.
- 2007 Daiichi-Sankyo, Ltd., Tokyo, Japan.
- 2008 Daiichi-Sankyo, Ltd., Tokyo, Japan.
- 2008 Novartis Oncology LEAD Summit VI, Montreal, Canada.

- 2009 Gairdner-Alberta Cancer Research Institute Symposium: "Research Advances in Our Understanding of the Biology and Treatment of Cancer," Edmonton, Alberta, Canada
- 2009 FEBS/EACR Advanced Lecture Course, "Molecular Mechanisms in Signal Transduction and Cancer", Spetses, Greece
- 2009 CNIO-Centro Nacional de Investigaciones Oncológicas: "Targeting the Ras Pathway", Madrid, Spain
- 2010 Institute of Predictive and Personalized Medicine of Cancer, Barcelona, Spain
- 2010 Vienna Biocenter Seminar, Vienna, Austria
- 2010 Cancer Genomics Centre / Centre for Biomedical Genetics Conference: "Molecular Mechanisms in Cancer," Amsterdam, The Netherlands
- 2010 Mitchell Lecture, Queen's University, Belfast, Ireland
- 2011 Lorne Cancer Conference, Lorne, Australia

**NATIONAL:**

- 1998 AACR, Molecular Biology and Pathology of Neoplasia, The Edward A. Smuckler Memorial Workshop, Keystone, CO
- 2002 University of Texas M. D. Anderson Cancer Center's 43<sup>rd</sup> Annual Clinical Conference "Drug Discovery and Clinical Evaluation in the 21<sup>st</sup> Century", Houston, TX.
- 2002 Cellular and Molecular Medicine, Graduate Training Program, School of Medicine, Johns Hopkins University, CMM Distinguished Lecture Series, Baltimore, MD.
- 2002 Harvard Center for Cancer Biology, Harvard Medical School, Harvard University, Distinguished Lecture Series, Boston, MA.
- 2002 Cold Spring Harbor Laboratory, Seminar Series, Cold Spring Harbor, NY.
- 2002 American Society of Clinical Oncology, Special ASCO Media Event: Meet the Expert, "Unlocking Cancer's Secrets: New Pathways to Targeted Treatments", New York, NY.
- 2002 Chicago Biological Signal Transduction Symposium 2002, Northwestern University Medical School, Chicago, IL.
- 2002 NNFF Consortium for the Molecular Biology of NF1 and NF2, "Tumorigenesis", Aspen, CO.
- 2002 2002 Rockefeller University Cancer Symposium, "A Vision for the Future: Molecular Approaches to Cancer Therapy", New York, NY.
- 2002 Gordon Research Conference on Chemotherapy of Experimental and Clinical Cancer, Bristol-Myers Squibb Pharmaceutical Research Institute. Colby-Sawyer College, New London, NH.
- 2002 University of Pittsburgh, Department of Biological Sciences, Pittsburgh, PA.
- 2002 University of Colorado, Cellular and Structural Biology, Health Sciences Center, School of Medicine, "Cells, Development and Cancer" Seminar Series, Denver, CO.
- 2003 Beth Israel Deaconess Medical Center and Harvard Medical School, Combined Grand Rounds, Department of Pathology and Division of Cancer Biology and Angiogenesis, Boston, MA.

- 2003 The University of Chicago, Cancer Research Foundation, Simon M. Shubitz Award Lecture, Chicago, IL.
- 2003 University of Washington, Biochemistry Department Graduate Student Seminar Series, Seattle, WA.
- 2003 National Institute of Health, National Cancer Institute, Critical Molecular Pathways Retreat, Wye River Conference Center, Queenstown, MD.
- 2003 Eli Lilly Cancer Discovery Research Seminar, Indianapolis, IN.
- 2003 Medical College of Georgia, Program in Molecular Medicine and Genetics, Augusta, GA.
- 2004 AACR/Japanese Cancer Association Joint Conference, Advances in Cancer Research, Waikoloa, HI.
- 2004 2004 Robert Sternlicht Lecture in Pharmacology and Hematology/Oncology, Case Western Reserve University, Cleveland, OH.
- 2004 Molecular and Cellular Basis of Disease Seminar, Cancer and Research Treatment Center, Department of Pathology, University of New Mexico, School of Medicine, Albuquerque, NM.
- 2004 "Meet the Expert" Sunrise Session, Progress in Oncolytic Viral Therapy, 95<sup>th</sup> Annual Meeting of the American Association for Cancer Research, Orlando, FL.
- 2004 National Institutes of Environmental Health Science, NIEHS, Martin Rodbell Memorial Lecture, Raleigh, NC.
- 2004 Vanderbilt University, Dept of Biochemistry, Vanderbilt-Ingram Cancer Center Research Education, Nashville, TN.
- 2004 The Foundation for Advanced Cancer Studies, Inc., 20<sup>th</sup> Annual Meeting on Oncogenes, Special Symposium, "New Therapeutics and Technologies", Hood College, Frederick, MD.
- 2004 Eli Lilly Cancer Discovery Research Seminar, Indianapolis, IN.
- 2004 The University of Texas M. D. Anderson Cancer Center, Blaffer Seminar Series, Department of Neuro-Oncology, Houston, TX.
- 2004 Cold Spring Harbor Laboratory, Keynote Speaker, Cancer Genetics & Tumor Suppressor Genes, Cold Spring Harbor, NY.
- 2004 University of Cincinnati Cancer Center Lecture Series, Department of Cell Biology, Neurobiology and Anatomy, Cincinnati, OH.
- 2004 Sideman Cancer Center, Barnes-Jewish Hospital, Washington University School of Medicine, Basic Science Seminar Series, St. Louis, MO.
- 2004 AACI, AACR, ASCO Joint Retreat, "Designing a Smart Clinical Trials System for the 21<sup>st</sup> Century: Optimizing the Interaction of Basic and Clinical Science," Lansdowne, VA.
- 2004 St. Jude Children's Research Hospital, Discoveries in Cancer Biology: From Science to Medicine Seminar, Memphis, TN.
- 2004 Bristol-Myers Squibb Company, Freedom to Discover Colloquium, Princeton, NJ.

- 2004 Association of American Cancer Institutes Annual Meeting, Chicago, IL.
- 2005 American Gastroenterological Association, 2005 Digestive Disease Week Chicago, IL.
- 2005 The University of Chicago Biomedical Sciences Cluster Committee on Cancer Biology Seminar Series, Chicago, IL.
- 2005 Memorial Sloan-Kettering Cancer Center, Charles B. Smith Visiting Research Professor, New York, NY.
- 2005 The 70<sup>th</sup> Cold Harbor Spring Harbor Laboratory Symposium: Molecular Approaches to Controlling Cancer, Cold Spring Harbor, NY.
- 2005 MIT Center for Cancer Research, Fourth Annual Symposium, Cambridge, MA.
- 2005 Baylor University Medical Center, Roundtable Discussion on Viral Gene Therapy of Human Cancers, Dallas, TX.
- 2005 National Cancer Institute and National Human Genome Research Institute, National Institutes of Health, Toward a Comprehensive Genomic Analysis of Cancer: A Roundtable Discussion, Washington, DC.
- 2005 The Salk Institute for Biological Studies, 5<sup>th</sup> Salk Institute/EMBL Oncogenes and Growth Control Meeting, La Jolla, CA.
- 2005 University of California, San Diego Medical Center, Moores Cancer Center Targeted Therapies in Oncology Symposium, San Diego, CA.
- 2006 The University of Texas, M. D. Anderson Cancer Center, Deborah M. Richman Memorial Lecture, Houston, TX.
- 2006 Winship Cancer Institute, Drug Development & Pharmacogenomics Academy, Emory University, Atlanta, GA.
- 2006 Abramson Family Cancer Research Institute, University of Pennsylvania, Philadelphia, PA.
- 2006 American Association for Cancer Research Annual Meeting, Chairperson, Drug Targets in the MAPK Pathway Symposium, Washington, DC.
- 2006 2006 Children's Tumor Foundation International Consortium for the Molecular and Cellular Biology of NF1, NF2 and Schwannomatosis, Progress: From Bench to Bedside, Aspen, CO.
- 2006 Bristol-Myers Squibb Company, Freedom to Discover Colloquium, Princeton, NJ.
- 2007 New York University Cancer Institute Seminar Series, New York, NY.
- 2007 Penn State Cancer Institute, 7<sup>th</sup> Annual Rod and Ceil Mortel Visiting Scholar in Cancer Research Symposium, Hershey, PA.

- 2007 Oregon Health & Science University, Medical Scientist Training Program Keynote Address Speaker, Portland, OR.
- 2007 American Association for Cancer Research Annual Meeting, Chairperson, Experimental and Molecular Therapeutics 15 Novel Agents Symposium, Los Angeles, CA.
- 2007 American Association for Cancer Research Annual Meeting, Cancer Biomarkers and Molecular Diagnostics Symposium Speaker, Los Angeles, CA.
- 2007 UCSF Department of Pediatrics 1<sup>st</sup> International Costello Syndrome Research Symposium 2007, Portland, OR.
- 2007 Halozyme Therapeutics, Inc., Seminar: "Success and failure of oncolytic viruses," San Diego, CA.
- 2007 Society for Melanoma Research, 2007 International Melanoma Congress, New York, NY.
- 2007 UCLA David Geffen School of Medicine, Department of Pathology and Laboratory Medicine, Seminar Series, Los Angeles, CA.
- 2008 Lombardi Comprehensive Cancer Center Oncology Grand Rounds, Georgetown University Medical Center, Washington, DC.
- 2008 Burnham Institute for Medical Research Center, Seminar Series Speaker, La Jolla, CA.
- 2008 The 19<sup>th</sup> Annual Cancer Progress Conference, Keynote Speaker, New York, NY.
- 2008 The Wistar Institute, Philadelphia, PA
- 2008 siRNA Consortium Spring Meeting, San Diego, CA
- 2008 American Association for Cancer Research Annual Meeting, Major Symposium: "Ras Signaling", San Diego, CA.
- 2008 City of Hope/UCSF collaboration and Team Presentation, "Ras as a Therapeutic Target", Duarte, CA.
- 2008 California Institute for Regenerative Medicine 2008 Cancer Stem Cells Workshop, Los Angeles, CA.
- 2008 Halozyme Therapeutics, Inc., On-site Collaboration Meeting, San Diego, CA.
- 2008 Association of American Cancer Institutes and Cancer Center Administrators Forum Annual Meeting, Invited Participant, Chicago, IL.
- 2009 M.D. Anderson, Invited Speaker, "Targeting the RAS Pathway", Houston, TX
- 2009 Kimmel Cancer Center, Grand Rounds, "Targeting the RAS Pathway", Philadelphia, PA
- 2009 AACR Annual Meeting, Invited Speaker, "Therapeutic Targeting the ras Pathways" and "Targeting the RAS Pathway", Denver, CO
- 2009 NCI/NIH/USDHHS Cancer Center Directors' Retreat, Arlington, VA

- 2009 City of Hope Graduate School of Biological Sciences, Commencement Speaker, Duarte, CA.
- 2009 2009 Neurofibromatosis Conference, Session Chair, "Unraveling the Signaling Culture-Pathways of NF", Portland, OR
- 2009 Yale Cancer Center, Grand Rounds, "Targeting the RAS Pathway", Princeton, NJ
- 2009 Cancer Institute of New Jersey, Distinguished Lecture Seminar, "Targeting the RAS Pathway", New Brunswick, NJ
- 2009 Vanderbilt Institute of Chemical Biology Retreat, Keynote Speaker, "Targeting the RAS Pathway", Nashville, TN
- 2009 6th Early Detection Research Network (EDRN), Scientific Workshop, "Impact of Early Detection on Targeted Therapy", Bethesda, MD
- 2009 The Brainstorming Event on The future of Cancer Therapy, Exelixis, Inc., Boston, MA
- 2009 AACI/CCAF Annual Meeting, Washington, D.C.
- 2009 Oncology Research and Development Symposium - Resistance to Targeted Therapies in Cancer, San Diego, CA
- 2009 AACR-NCI-EORTC - Molecular Targets and Cancer Therapeutics: Discovery, Biology and Clinical Applications, Boston, MA.
- 2010 Children's Tumor Foundation Consortium Retreat, Santa Monica, CA
- 2010 AACR 2010 Program Committee Meeting, Philadelphia, PA
- 2010 UCLA Institute for Molecular Medicine Seminar, UCLA, Los Angeles, CA
- 2010 Translational Cancer Research Seminar Series, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH
- 2010 AACR Annual Meeting, Washington, DC
- 2010 ASCO Annual Meeting, Science of Oncology Award, Chicago, IL
- 2010 AACI Clinical Research Initiative Meeting, Chicago, IL
- 2010 The University of Texas MD Anderson Cancer Center Grand Rounds, Houston, TX
- 2010 AACR Translational Cancer Research for Basic Scientists Workshop, Boston, MA
- 2011 Amgen Oncology Seminar Series, Thousand Oaks, CA
- 2011 Gordon Research Conference – "Cancer Genetics & Epigenetics," Ventura Beach, CA

**REGIONAL AND OTHER INVITED PRESENTATIONS:**

2002	AACR - A.G.H. Clowes Memorial Award Lecture, AACR Annual Meeting, San Francisco, CA.
2002	AGA Research Symposium "Colon Cancer: APC-beta Catenin Pathway", San Francisco, CA.
2002	XIVth World Congress of Pharmacology, "Cancer Therapy Based on Ras and related proteins", San Francisco, CA.
2002	University of California, School of Medicine, Dean's Seminar Series, UCSF.
2002	University of California, Department of Biochemistry and Biophysics and the Hillblom Center for the Biology of Aging, Cancer Mini Symposium, "The War on Cancer: Where are We?" San Francisco, CA.
2002	University of California, School of Medicine Graduate Programs: Department of Biochemistry & Molecular Biology, Genetics, Cell Biology and Developmental Biology, 2002 TETRAD Scientific Conference at Granlibakken, Lake Tahoe, CA.
2003	The Seventh International Biotech Summit, Innovation and The Marketplace: New Risks, New Rewards, University of California, San Francisco, CA.
2003	Lawrence Berkeley National Laboratory, Life Sciences Division Seminar, Berkeley, CA.
2004	University of California, San Francisco, Department of Surgery, 3 <sup>rd</sup> Annual Clinical Cancer Update, Lake Tahoe, CA.
2005	Stanford University School of Medicine, Tumor Biology Training Program, Stanford, CA.
2005	The Early Detection Symposium, Canary Fund, Stanford University, Stanford, CA.
2005	National Cancer Institute, Integrative Cancer Biology Program Mini-Symposia Berkeley, CA.
2005	University of California in San Francisco, 7 <sup>th</sup> Annual Osher Lifelong Learning Institute and Mini Medical School, "Cancer Biology 101: Clues About New Treatments and Early Detection", UCSF.
2006	Amgen San Francisco, Seminar: "Therapeutic Approaches to Ras", South San Francisco, CA.
2006	Theravance Cancer Symposium, South San Francisco, CA.
2006	Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA.
2006	UCSF Mini Medical School for the public course "Cancer: Bench to Bedside", UCSF.
2007	Novartis Seminar: "Drug targets in the Ras pathway," Emeryville, CA.
2007	UCSF Biomedical Sciences Graduate Program Session: "Cancer Biology and Cell Signaling and Tissue/Organ Biology & Endocrinology", UCSF.
2007	UCSF Department of Pathology: "Molecular Pathology and Biology of Neoplasia Course", UCSF.

- 2007 American Association for Cancer Research Translational Cancer Medicine Think Tank, Sonoma, CA.
- 2007 Stanford Cancer Center and Stanford University School of Medicine, Comprehensive Cancer Research Training Program Keynote Address, Stanford, CA.
- 2007 Stanford Medical School Cancer Biology Retreat Keynote Speaker, Palo Alto, CA.
- 2008 Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA.
- 2008 UCSF Cancer Club, Therapeutics Challenges of Melanoma, UCSF.
- 2008 UCSF Herbert W. Boyer Program in Biological Sciences (PIBS), 1<sup>st</sup> Year Students Lecture: "Ras signaling in normal cells and cancer," San Francisco, CA.
- 2008 UCSF Helen Diller Family Comprehensive Cancer Center 2008 Symposium: Stem Cells and Cancer, San Francisco, CA.
- 2009 UCSF Emeriti Faculty Association: "Targeting the Ras Pathway.", San Francisco, CA.
- 2009 UCSF 3<sup>rd</sup> International Symposium on Cancer Metastasis and the Lymphovascular System: Basis for Rational Therapy: "Cancer Therapy based on Oncogene Action", San Francisco, CA.
- 2009 Molecular Therapeutics of Cancer Research Conference 2009: Session Leader "Oncogene Addiction", Stanford, CA.
- 2009 Genetic Syndromes of the Ras/MAPK Pathway: From Bedside to Bench and Back, Keynote Speaker: "New Perspectives on an Ancient Pathway", Berkeley, CA
- 2009 UCSF Workshop on Nutrition, Translational Medicine and Prostate Cancer, San Francisco, CA
- 2009 UCSF Helen Diller Family Comprehensive Cancer Center 2009 Symposium: The Prevention of Cancer, San Francisco, CA
- 2009 Population Sciences Special Interest Group (PopSci SIG) Face-to-Face Meeting hosted by HDFCCC and the NCI, San Francisco, CA
- 2010 UCSF Pancreas Cancer Program Retreat, San Francisco, CA
- 2010 AACR Think Tank on Clinical and Translational Cancer Research, San Francisco, CA
- 2010 2010 UCSF Breast Oncology Program Scientific Retreat, San Francisco, CA
- 2010 Society for Basic Urologic Research / Society of Urologic Oncology Spring Meeting, San Francisco, CA
- 2010 UCSF Prostate Cancer Program Retreat, San Francisco, CA
- 2010 Novartis Institute for Biomedical Research Seminar, Emeryville, CA



2010	UCSF Clinical and Translational Science Planning Meeting, San Francisco, CA
2010	Stanford Cancer Center and Stanford University School of Medicine, Comprehensive Cancer Research Training Program Plenary Lecture, Stanford, CA
2010	UCSF Cancer, Immunity & Microenvironment Symposium, San Francisco, CA
2010	UCSF Biomedical Sciences Retreat, Lake Tahoe, CA
2010	USF Cancer Research Translational Medicine Seminar, San Francisco, CA
2010	UCSF Helen Diller Family Comprehensive Cancer Center Symposium on Biology and Treatment of Brain Cancers, San Francisco, CA
2011	UCSF Breast Oncology Program Scientific Retreat, San Francisco, CA

**CME COURSES ATTENDED:** Not Applicable

**GOVERNMENT and OTHER PROFESSIONAL SERVICE:**

1996	National Cancer Institute Working Group of Preclinical Models for Cancer
1997-now	National Cancer Center Directors Working Group
1998-1999	National Cancer Institute Developmental Therapeutics Program Scientific Advisory Board
1998-2003	National Cancer Institute Board of Scientific Counselors Advisory Committee
2003-now	National Cancer Institute Initiative for Chemical Genetics External Scientific Committee
2004-now	National Cancer Institute Integrative Biology Program

**UNIVERSITY AND PUBLIC SERVICE:**

**UNIVERSITY SERVICE:**

**SYSTEMWIDE:**

2002-2003	University of California, Irvine-Cancer Center	External Advisory Board
2001-now	University of California Cancer Centers Consortium	Member

**UCSF CAMPUS-WIDE:**

1998-now	Mount Zion Subcommittee, Chancellor's Advisory Committee on the 2002 LRDP Amendment Sokolow Memorial Cancer Endowment Lectureship Committee, Chair
2002-2003	Parnassus Heights Leadership Council
2002-now	Academic Planning Subcommittee, Chancellor's Advisory Committee on the Long Range Development Plan Amendment (Hospital Replacement)
2006-now	UCSF's Strategic Planning Initiative Board Member and Subcommittee Member: Strategy Design Team B-Research Directions

**SCHOOL OF MEDICINE:**

1998	LCME Subcommittee on Research, and Graduate Education in Basic Sciences	
1998-now	Biomedical Sciences Program (BMS)	Member
1998-now	Herbert Boyer Program in Biological Sciences (PIBS)	Member
1999-2001	Preuss Molecular Neuro-Oncology Search Committee	Member
2000-2003	Developmental Research and Fellowship Committee	Member

	(Department of Urology)	
2000-now	Executive Committee Prostate Cancer SPORE	Member
	(Department of Urology)	
2000-now	Advisory Review Committee Prostate Cancer SPORE	Member
	(Department of Urology)	
2000-now	Prostate Cancer Career Development Program	Ad Hoc Member
	(Department of Urology)	
2002	School of Medicine, Hematology Oncology Faculty Search Committee	Member
2002-2003	Academic Planning Subcommittee of the Chancellor's Advisory Committee on the LRDP Amendment	Member
2002	School of Medicine, Microbiology Faculty Search Committee	Member
2002-2003	School of Medicine, Dean's Search Committee	Member
2003-now	School of Medicine Medical Scientist Training Program	Faculty Advisor
2003-now	Brain Tumor Research Center, Department of Neurological Surgery	Associate Member
2004	School of Medicine, Chair of the Department of Obstetrics, Gynecology and Reproductive Sciences Search Committee	Member
2005-2007	CTSA Senior Leadership Group Committee	Member
2005-2007	School of Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences Director, Division of Gynecologic Oncology	Member
2006-now	Pharmacogenetics of Membrane Transporters Scientific Advisory Board	Member
2006-2006	School of Medicine, CTSI Principal Investigator Search Committee (Department of Medicine)	Member
2006-2007	School of Medicine, CTSI Executive Director Search Committee (Department of Medicine)	Member
2006-2007	School of Medicine, Radiation Oncology Search Committee (Department of Medicine)	Member
2006-2007	School of Medicine, Chair, Department of Medicine Search Committee	
2007-now	School of Medicine, Hematology and Oncology Division Chief Search Committee (Department of Medicine)	Member
2008-now	School of Medicine, Dean's Search Committee	Member
2008-now	Pancreas SPORE Internal Advisory Board	Member
	(Department of Medicine, Division of Hematology and Oncology)	
2009	Department of Medicine, OB/Gyn & RS Search Committee for Assistant/Associate Professor in Residence, Division of Gynecologic Oncology	Member
2009	Department of Medicine, Division of Hematology and Oncology, Search Committee for Assistant/Associate Professor in-Residence, Urologic Oncology	Member
2009	Office of the Vice Chancellor Search Committee, Executive Director of Research Resource Program	Member
2010	School of Medicine, Hematology and Oncology Professor In-Residence Search Committee	Member
2011	School of Medicine, Department of Urology Urologic Oncology Faculty Search Committee	Member
2011	Waxman Foundation Award Selection Committee	Member

**DEPARTMENTAL SERVICE:****Helen Diller Family Comprehensive Cancer Center:**

1997-1999	Laboratory Sciences Steering Committee	Member
1997-now	American Cancer Society Institutional Research Grant Program Award Review Committee	Member
1998-now	Mount Zion Health Fund Institutional Research Award Review Committee	Member
1998-now	Directors Group	Chair
1998-now	Executive Committee	Chair
1998-now	Program Leaders Committee	Chair
1998-now	Prostate Cancer Program Steering Committee	Chair
1998-now	Scientific Advisory Council, Lab Sciences Committee	Chair
1999-now	Breast Oncology Program	Program Member
1999-now	Cell Cycling and Signaling	Program Member
1999-now	Maurice, Ethel, and Jane Sokolow Memorial Cancer Endowment Committee	Chair
1999-now	Alexander and Margaret Stewart Trust Endowment Committee	Chair
2000-now	Cancer Research Building Space Review Committee	Chair
2003-2008	Clinical Cancer Center Governing Board	Chair
2000-2001	Search Committee for Associate Director of Education and Outreach	Chair
2000-2001	Search Committee for Associate Director of Epidemiology Prevention and Control	Chair
2001-now	Critical Players at Mount Zion Committee	Member
2005-now	UCSF Helen Diller Family Comprehensive Cancer Center Community Advisory Board	Member
2007	Cancer Center Naming Event Ad Hoc Committee	Member
2008	Diller Governance Building Committee	Member

**PUBLIC SERVICE:****Fundraising**

2006 - \$150 Million Pledge for the UCSF Helen Diller Family Comprehensive Cancer Center. Participated in 22 months of negotiations resulting in a gift of \$150M. Met with the donors and UCSF leadership to define the vision and craft a proposal that aligned the needs of the Center with the interests of the donor to secure the gift.

On average, participated in approximately 30 donor solicitation visits annually. Since 2003, solicitations were done in support of the Mission Bay Campaign, the Cancer Research Building Campaign, Atwater Projects for Breast Cancer, and the ongoing solicitation of gifts for the programs, faculty, and general support of the Center.

Participated in quarterly planning meetings to review strategy for direct mail and programmatic fundraising efforts to benefit the Cancer Center general fund. In the first year, this program produced net revenue of approximately \$70,000 and, in year five years, it is producing approximately \$450,000 net revenue. The program now includes an option for donors to direct gifts to programmatic areas of the Center and the costs are underwritten by the Helen Diller Family Comprehensive Cancer Center.

Monthly meetings with the development staff. Fundraising for Cancer at UCSF has risen from \$28 million in FY03 to \$61 million in FY07.

Donor Stewardship and Institutional Service

On average, participated in 24 donor stewardship activities annually to maintain relationships with principal and major donors to the Helen Diller Family Comprehensive Cancer Center. One such donor is now a major donor (\$25M) to the new hospital campaign.

- Since 1996      Participated in the biennial "Raising Hope" benefit for the UCSF Helen Diller Family Comprehensive Cancer Center. Attended, presented, and purchased a table at each of six Raising Hope events held to date. In 2007, the sixth event raised over \$3.75M. Since inception the event has raised awareness and over \$21M for the Cancer Center.
- Since 1999      Presenter at the annual UCSF Helen Diller Family Comprehensive Cancer Center Symposium
- Since 2003      Presented at Cancer Council meetings and met with several Cancer Council members each year
- May 2004      Spoke at the opening of the AVON Foundation Comprehensive Breast Center, a state-of-the-art woman's imaging center at San Francisco General Hospital
- Since 2005      Speaker at the Annual Canary Foundation National EDI Stakeholders Symposium and participate in the Annual Canary Foundation's Gala Event "Cabana". In 2006, participated in The Canary Foundation CXO and Celebrity Go-Kart Challenge and recruited a race car driver to participate in the event and sponsor a \$10,000 table for the 2006 Cabana gala event.
- Feb 2006      Salute to Excellence Awards Gala, American Liver Foundation. Personally sponsored a \$5,000 table on behalf of the UCSF Comprehensive Cancer Center.
- May 2007      Attended Welcome Reception of the National Association of Cancer Center Development Officers and Public Affairs and Marketing Network Conference
- July 2007      Attended UCSF Advancement Resources Development Workshop
- Nov 2007      Speaker at the naming event for the Helen Diller Family Comprehensive Cancer Center
- Nov 2007      Speaker in a DVD presented at the Foundation Annual Meeting
- Feb 2008      Speaker at the Mount Zion Auxiliary Board of Directors Meeting
- Feb 2008      Attended the Paving the Way 2008 event in benefit of the Larkin Street Youth Services
- Mar 2008      Participated in the 2-day Atlantic Philanthropies Symposium
- Apr 2008      Presented and co-hosted a table at the Chancellor's Dinner held at SFMOMA

Foundation Advisory Boards:

- 2004-now      Canary Foundation Scientific Advisory Board

2006-now      Melanoma Research Foundation Board Member and Scientific Advisory Board

### **TEACHING and MENTORING:**

#### **FORMAL SCHEDULED CLASSES FOR UCSF STUDENTS:**

Qtr	Academic Yr	Course No & Title	Teaching Contribution	Class size
Winter	2004	Biochem 297: Molecular Pathology and Biology of Neoplasia	Lecture	25
Fall	2006	Cancer Block IDS 106: Cancer: Bench to Bedside (CBB)	Lecture: Frontiers in Cancer Therapy	35
Winter	2007	Biochem 297: Molecular Pathology and Biology of Neoplasia	Lecture: New Approaches to Cancer Treatment & Rational Therapy	25
Winter	2007	UCSF Herbert W. Boyer Program in Biological Sciences (PIBS), 1 <sup>st</sup> Year Students Lecture	Lecture: Ras signaling in normal cells and cancer	25

#### **POSTGRADUATE AND OTHER COURSES:**

Qtr	Academic Yr	Course No & Title	Teaching Contribution	Class size
Winter	2004	MSU04004: 3 <sup>rd</sup> Annual UCSF Clinical Cancer Update, Department of Surgery	Lecture: Cancer Therapy Based on Oncogenes and Tumor Suppressors	50-75
Summer	2005	Elective: UCSF Mini Medical School for the Public	Lecture: New Horizons on the War on Cancer: Theory to Therapy	75-100
Fall	2005	MLL06001: UCSF Mini Medical School for the Public, Cancer Biology 101: Clues About New Treatments and Early Detection	Lecture: New Treatments and Early Detection	75-100
Summer	2007	MMC08003: 1 <sup>st</sup> International Costello Syndrome Research Symposium 2007	Session Moderator: Treatment Modalities Lecture: Overview to Treatment Options	150-200

#### **STUDENTS SUPERVISED OR MENTORED:**

Dates	Name	Fellow	Faculty Role	Current Position
Spring 2009	Phillip Greyling	Spring Intern	Advisor	Student – UC Santa Cruz
2009	Vritti Goel	Summer Intern	Advisor	Student – Scripps College, Claremont, CA
2009	Alison Altman	Summer Intern	Advisor	Student – Yale College, New Haven, CT

#### **PREDOCTORAL STUDENTS SUPERVISED OR MENTORED:**

Dates	Name	Fellow	Faculty Role	Current Position
1997	Eric Collisson, MD	Summer Intern	Advisor	Senior Fellow, Div. of Hematology/Oncology, UCSF
1999-2000	Kenichi Wakita	Daiichi-Sankyo, Ltd	Masters, 1989, Tokyo Institute of Technology	Staff Scientist, Daiichi-Sankyo, Ltd.
Spring 2001	Michelle Shih	UCSF Biomedical Sciences Program	Rotation Advisor	2007 Graduate
Spring 2001, Fall 2001-Summer 2006	Demetris Iacovides	UCSF Biomedical Sciences Program	Thesis Advisor (joined lab Fall 2001)	Post-doctoral Fellow, Lawrence Berkeley National Laboratory, Gray Lab
Fall 2001	Curtis Pickering	UCSF PIBS Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Summer 2002	Felicia Yen	High School Summer Intern	Supervisor	Undergraduate, Harvard University
Fall 2002	Jaime Lopez	UCSF-SFSU PREP	Rotation Advisor	UCSF Cancer Research

		Program		Institute, Toczyski Lab
Winter 2002	Erika Woodbury	UCSF PIBS Program	Rotation Advisor	Postdoctoral Scholar, McCormick Lab, UCSF
Winter 2002	Yong Ping Crawford	UCSF Biomedical Sciences Program	Rotation Advisor	Unknown
Winter 2003, Summer 2003-present	Abigail Miller	UCSF Biomedical Sciences Graduate Program	Thesis Advisor (joined lab Summer 2003)	UCSF Cancer Research Institute, McCormick Lab
Spring 2003, Summer 2003-present	Cynthia Mysinger	UCSF Biomedical Sciences Program	Thesis Advisor (joined lab Summer 2003)	Pre-doctoral Scholar, UCSF
Fall 2003	Cory Nicholas	UCSF Biomedical Sciences Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Fall 2003	Mina Nikanjam	UCB - Bioengineering	Rotation Advisor	Unknown
Fall 2003-Winter 2008	Vernon Phan	UCSF Biomedical Sciences Program	Thesis Advisor (joined lab Winter 2003)	Post-doctoral Fellow, Genentech, Inc.
Winter 2004	Vanessa Angeles	UCSF Biomedical Sciences Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Spring 2004, Summer 2004-present	Jesse Lyons	UCSF Biomedical Sciences Program	Thesis Advisor (joined lab Summer 2004)	UCSF Cancer Research Institute, McCormick Lab
Summer 2004, Fall 2005-Spring 2007	Ammanuel Asmamaw	UCLA Graduate/UCSF-SFSU PREP Program	Rotation Advisor	Research Associate, Department of Surgery, Stanford University
Fall 2004	Michael D'amborasia	UCSF PIBS Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Fall 2004-present	Amy Young	UCSF Biomedical Sciences Program	Thesis Advisor	UCSF Cancer Research Institute, McCormick Lab
2005-2007	Jennifer Okada	UCLA Graduate/CRI Junior Specialist	Supervisor	Research Associate, Exelixis, Inc.
2005-2007	Mayumi Kitagawa	Daiichi-Sankyo, Ltd/CRI Assistant Specialist	Supervisor	Staff Scientist, Daiichi-Sankyo, Ltd.
Fall 2005	Alana Lerner	UCSF Biomedical Sciences Graduate Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Fall 2005	Nichole Reyes	UCSF Biomedical Sciences Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Fall 2005	Noel Moreno	UCSF-SFSU PREP Program	Rotation Advisor	San Francisco State University Graduate Student
Fall 2005, Fall 2006-present	Michael Nehil	UCSF TETRAD Program	Thesis Advisor (joined lab Winter 2006)	UCSF Cancer Research Institute, McCormick Lab
Summer 2006	Frank Bos	University Medical Center, Utrecht	Internship Rotation Advisor	Pre-doctoral Scholar, Utrecht, The Netherlands
Summer 2006, Fall 2006-present	Irma Rangel	UCSF TETRAD Program	Thesis Advisor (joined lab Winter 2006)	UCSF Cancer Research Institute, McCormick Lab
Fall 2006	Jeffrey Alexander	UCSF Biomedical Sciences Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Fall 2006	Renee Vanderlaan	UCSF Biomedical Sciences Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Summer 2006-present	Daniel Garcia	UCSF Biomedical Sciences Program	Thesis Advisor	Pre-doctoral Scholar, UCSF
Fall 2007	Angela Rojas	UCSF Biomedical Sciences Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Fall 2009-present	Kegan Warner	UCSF Biomedical Sciences Program	Thesis Advisor	Pre-doctoral Scholar, UCSF
Fall 2009-present	Danielle Shin	UCSF Biomedical Sciences Program	Thesis Advisor	Pre-doctoral Scholar, UCSF
Winter 2010	Joseph Juan	UCSF TETRAD Program	Rotation Advisor	Pre-doctoral Scholar, UCSF
Winter 2010	Lawrence Lin	UCSF - Pharmaceutical Sciences and	Rotation Advisor	Pre-doctoral Scholar, UCSF

		Pharmacogenomics		
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**POSTDOCTORAL FELLOWS AND RESIDENTS DIRECTLY SUPERVISED:**

Dates	Name	Prior Academic Degree	Title of Research Project	Faculty Role	Current Position
1975-present	Madhu Macrae	Ph.D., 1997 UCSF Microbiology	A Potential New Approach to Targeted Cancer Therapy	Research Advisor	Specialist, UCSF Cancer Research Institute
1996-2000	Rui-hong Chen	Ph.D., 1994, SUNY Stony Brook, NY	Regulation of $\beta$ -catenin and colon cancer therapeutics	Research Advisor	Staff Scientist, Nexgenix Pharmaceuticals, LLC
1997-1999	Osamu Tetsu	M.D., 1989, Ph.D., 1997, Chiba University, Japan	$\beta$ -catenin regulated cyclin D1 expression in colon carcinoma cells	Research Advisor	Assistant Adjunct Professor, Department of Otolaryngology, Head & Neck Surgery, UCSF
1997-2000	Jingwu Xie	Ph.D., 1994, Dundee University	The hedgehog signaling pathway and human cancer	Research Advisor	Associate Professor, University of Texas Medical Branch
1997-2001	Peter Sabbatini	Ph.D., 1997, Rutgers University, NJ	PKB & p53 dependent apoptosis	Research Advisor	Staff Scientist, Celera Corporation
1997-2002	Wei Vivianne Ding	Ph.D., 1997, University of Texas, Southwestern Medical Center	Regulation of GSK3 in cancer cells and Wnt signaling pathway	Research Advisor	Assistant Researcher, UCSF Department of Surgery
1997-2007	Pablo Rodriguez-Vician	Ph.D., 1997, University College, London	Role of PI 3 Kinase in Ras induced tumor genesis	Research Advisor	Associate Professor, University College of London, UK
1997-1998	Michael Korn	M.D., 1988, University of Dusseldorf	Adenovirus tumor cell interaction	Research Advisor	Associate Professor of Medicine, Department of Gastroenterology, UCSF
1997-2000	Katherine A. Rauen	Ph.D., 1992, MD, 1995, UC Davis	Mouse model for E1b55k deleted mouse adenovirus	Research Advisor	Adjunct Professor, Department of Pediatrics, UCSF
1997-2001	Haiyan Jiang	Ph.D., 1997, University of Wisconsin Madison	Mechanism of parvovirus induced the cell killing in human transformed cells	Research Advisor	Staff Scientist, Amgen Corporation
1998-2001	Stefan Ries	Ph.D., 1998, University of Regensburg, Bavaria	Mechanisms of 015 replication in colon cancer cell lines	Research Advisor	Staff Scientist, MediGene, Munich, Germany
1998-2006	Clodagh O'Shea	Ph.D., 1997, Imperial College of Science & Technology, University of London	The role of PML in viral replication and oncogenesis and adenoviral replication in primary cells	Research Advisor	Assistant Professor, UCSD, The Salk Institute
1998-1999	Christopher Haqq	M.D., 1996, Ph.D., 1996, Harvard Medical School	Prostate Cancer Gene Expression	Research Advisor	Assistant Adjunct Professor, Department of

					Urology, UCSF/Sr. Director of Clinical & Research Development, Cougar Biotech, Inc.
1998-1999	Tomoko Tominaga	M.D., 1984, Ehime Univ. Faculty of Medicine, Ph.D. 1993 Kyoto Univ. Faculty of Medicine	Studies of diaphanous related formins as Rho effector proteins	Research Advisor	Professor, Dept of Bio-Environmental Science, Cell Signaling, National Institute for Physiological Sciences, Aichi, Japan
1999-2001	Carola Biederer	Ph.D., 1999, University of Aachen	Role of Ras induced MDM2 in tumor genesis	Research Advisor	Staff Scientist, Roche, Munich, Germany
1999-2007	Luika Timmerman	Ph.D., 1998, Stanford University	Wnt signaling in the mammary gland	Research Advisor	Assistant Research Molecular Biologist, UCSF Cancer Research Institute
2000-2003	Masashi Aonuma	Ph.D., 1999, Tokyo University	Analysis of ARF expression	Research Advisor	Manager, Biological Research Laboratories, R&D Division, Daiichi-Sankyo, Ltd.
2001-2003	Jay Gump	Ph.D., 2001 Univ. of Vermont	Post-translational regulation in the CDK4 pathway	Research Advisor	Consultant, Unknown Company Profile
2001-2004	Jennifer Yeh	Ph.D., 2001, University of Texas	Microarray analysis of gene expression in breast cancer	Research Advisor	Consultant, Unknown Company Profile
2002-present	Sang-Hyun Lee	Ph.D., 2002, Univ. of MO-Columbia	P53 ARF pathway Analysis	Research Advisor	National Research Foundation Fellow/Singapore
2002-2005	Hiroshi Okabe	Ph.D., 2001, Kyoto University, Japan	Mechanisms of cyclin D1 proteolysis	Research Advisor	Laboratory Medicine, Human Genome Center, University of Tokyo, Japan
2004-2005	Jimbo Takeshi	Ph.D., 2002, University of Tokyo	Cancer research focusing on preclinical and clinical biomarkers for potent MDM2 inhibitors	Research Advisor	Staff Scientist, Daiichi-Sankyo Ltd., Japan
2004-2008	Anthony Karnezis	M.D., Ph.D., 1996, 2002, Northwestern University/ Albert Einstein College of Medicine	Lung Cancer: Small cell and non-small cell	Research Advisor	Postdoctoral Scholar, UCSF Cancer Research Institute
2004-2006	Seiko Ishida	Ph.D., 2001, UCSF	Studying the mechanism by which cells become addicted to Ras through suppression of apoptosis	Research Advisor	Assistant Research Biochemist, UCSF Cancer Research Institute
2005-2007	Katsutoshi Oda	M.D., Ph.D., 1994, 2001, University of Tokyo	Cancer research focusing on preclinical and clinical biomarkers for potent MDM2 inhibitors	Research Advisor	Associate Professor, Department of Obstetrics & Gynecology, University of Tokyo, Japan



2007-2010	Erika Woodbury	Ph.D. 2007, UCSF PIBS Program	Investigation of the role of the tumor suppressor protein neurofibromin in the DNA damage response	Research Advisor	Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center
2007-2008	Heather Christofk	Ph.D., 2007, Harvard Medical School	Metabolic Changes in Cancer Cells	Research Advisor	Asst. Professor, Inst. for Molecular Med. (IMED), UCLA
2007-present	Takahiko Seki	Ph.D., 2002, University of Tokyo	Involvement of MdmX in Nutlin-sensitivity	Research Advisor	Associate Specialist, UCSF Cancer Research Institute/Daiichi-Sankyo, Ltd.
2008-present	Matthew Holderfield	Ph.D., 2007, UC Irvine	Signaling pathways downstream of Ras	Academic Mentor	Postdoctoral Scholar, Novartis Institutes for Biomedical Research
Spring 2003, Summer 2003-2010	Cynthia Mysinger	Ph.D. 2009, UCSF Biomedical Sciences Program	Thesis Advisor (joined lab Summer 2003)	Research Advisor	Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center
2008-present	Tanja Tamguney	PhD	Self-amplifying plasmids for cancer therapy	Research Advisor	Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center
2010-present	Tina L. Yuan	PhD		Research Advisor	Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center
2010-present	Ellen O'Dea	PhD		Research Advisor	Postdoctoral Scholar, UCSF Helen Diller Family Comprehensive Cancer Center

**INFORMAL TEACHING:**

1999-now	Bimonthly research advisor/mentor meetings with graduate students and postdoctoral scholars/fellows
1999-now	Weekly laboratory meetings (graduate students and postdoctoral scholars/fellows)
2006	Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA.
2008	Lick-Wilmerding High School, Honors Biology: Genetics and Evolution Class, San Francisco, CA.
2008-now	Quarterly meetings with Post-doctoral Scholar from the Novartis Institutes for Biomedical Research Postdoctoral Program

**FACULTY MENTORING****FACULTY MENTORED:**

Dates	Name	Position while Mentored	Mentoring Role	Current Position
2007-now	John K. Chan, MD	Assistant Professor	Assigned Faculty Mentor/Advisor	Assist Prof, OB, GYN & Reproductive Sci, UCSF
1997-now	W. Michael Korn, MD	Postdoc and now Associate Professor	Research Advisor/Co-Investigator on U54 grant	Associate Prof, Div of GI & Med Onc, UCSF
1997-now	Osamu Tetsu, MD, PhD	Postdoc and now Assistant Adjunct Professor	Academic and Research Advisor	Assist Adjunct Prof, Dept of Otolaryngology, Head & Neck Surgery, UCSF
1999-now	David Jablons, PhD	Assistant Professor of Surgery	Research Advisor/Scientific Collaborator	Ada Distinguished Prof of Thoracic Onc, Dept of Surgery, UCSF
1997-now	Katherine A. Rauen, MD, PhD	Postdoc and now Adjunct Professor	Research Advisor/Co-sponsor on K23 Grant	Assistant Adjunct Professor, Dept of Pediatrics, Div of Medical Genetics, UCSF

**OTHER VISITING FACULTY SUPERVISED:**

Dates	Name	Position while Mentored	Mentoring Role	Current Position
1998-1999	Pierre Chardin, PhD	Visiting Scholar	Research Advisor	Researcher, Institut de Pharmacologie du CNRS, France
1999-2000	Michael Fried, PhD	Visiting Scholar-Sabbatical	Research Advisor	Adjunct Professor, UCSF Cancer Research Institute
2002	Alexander Levitzki, PhD	Visiting Scholar-Sabbatical	Research Advisor	Professor, The Institute of Life Sciences, The Hebrew University of Jerusalem
2005	Giannoulis Fakis, PhD	Visiting Scholar-Sabbatical	Research Advisor	Lecturer, Democritus University of Thrace, Dept of Molecular Biology and Genetics, Greece
2006	Giannoulis Fakis, PhD	Visiting Scholar-Sabbatical	Research Advisor	Lecturer, Democritus University of Thrace, Dept of Molecular Biology and Genetics, Greece
2008-2009	Laura van 't Veer, PhD	Visiting Scholar-Sabbatical	Research Advisor	Professor, The Netherlands Cancer Institute

**TEACHING AIDS:**

UCSF: 2006 Cancer Block IDS 106: Cancer: Bench to Bedside (CBB), Frontiers in Cancer Therapy Lecture Syllabus for 2<sup>nd</sup> year medical students and exam questions.

**OTHER:**

See visiting Professorships and service lectures listed under "Invited Presentations"

**TEACHING AWARDS AND NOMINATIONS:**

See Honors and Awards

**SUMMARY OF TEACHING HOURS: (including preparation)**

2007-now      563 total hours of teaching and mentoring  
                     Formal Class or course teaching hours: 23 hours  
                     Informal teaching hours: 180 hours  
                     Mentoring hours: 360 hours

2008-2009:      Total anticipated hours of teaching and mentoring: 563 hours (as above)

**TEACHING NARRATIVE:**

My recent teaching activities have been dedicated to two roles: research advisor and mentor to faculty, graduate students, and postdoctoral scholars. I have taught and supervised 32 pre-doctoral students, 31 postdoctoral scholars/fellows, 5 faculty members, and 5 visiting scholars. I have taught scientific concepts and techniques during weekly meetings with my laboratory members and closely supervised the work of postdoctoral researchers in my lab at the UCSF Helen Diller Family Comprehensive Cancer Center. Three postdocs from my lab have stayed at UCSF (Drs. Korn, Rauen, and Tetsu) and I continue to mentor them, assist them with grants and papers, and collaborate where appropriate. Recently, Dr. Rauen published in *Science*, assisting her at several levels. Dr. Tetsu has published highly cited papers in *Nature* and *Cancer Cell*. Dr. Korn has published in *PNAS* and *Nature Medicine*. Recently, I have cut down the number of institutions and companies that I consult for to spend more time with my students and postdocs, as well as mentoring junior faculty. I participate in Cancer Club, PIBS, BMS, etc., and serve as faculty advisor to the MSTP program.

**RESEARCH AND CREATIVE ACTIVITIES****RESEARCH AWARDS AND GRANTS:****CURRENT**

P30 CA82103 McCormick (PI)	09/25/2007-05/31/2012
NIH/NCI	\$3,624,403 direct/yr 1
Cancer Center Support Grant	\$19,550,266 Total direct/yr 1-5
The Cancer Center Support Grant provides support for administration and infrastructure for the UCSF Comprehensive Cancer Center. Dr. Frank McCormick is the Director of the Cancer Center.	

Daiichi-Sankyo Pharmaceuticals Contract (PI)	8/06/2004 – 2/1/2011
Preclinical Evaluation of Drugs that Inhibit Mdm2	\$594,060 direct/yr 1
The major goal of this project is to develop inhibitors of Mdm2 as cancer therapeutics.	\$1,274,250 Total direct/yr 1-3

American Assn for Cancer Research (PI)	7/1/2010-6/30/2012
Specific K-Ras Inhibitors for treating pancreatic cancer	\$180,000 direct/yr 1-2
The major goals of this project are to propose a new effort to target the C-terminus of K-Ras 4B, the major form of K-Ras expressed in pancreatic cancer cells, by identifying small molecules that bind to this region and covalently modify cysteine-186 to prevent lipid modification and block K-Ras 4B function in cancer cells.	

U54CA143836 (Liphardt)(Co-Investigator)	9/29/2009-7/31/2014
UC Berkeley	\$80,239 direct/yr 1
Fundamental Mechanobiology of Tumor Progression	\$423,527 Total direct/yr 1-5
The major goals of this project are to evaluate potential therapeutic applications of the projects and addressing questions that of highest clinical impact	

**PENDING**

Lustgarten Foundation (PI)	11/1/2010 - 10/31/2013
	\$166,666 direct/yr 1
	\$661,146 Total direct/yr 1-3
The major goal of this project is to develop and utilize human antibody-targeted nanoparticles to deliver small interfering RNAs to pancreatic tumor cells to inhibit K-ras function.	

## **PAST**

BIO07-10642-IND (PI) 2/1/2008 - 1/31/2011  
 Halozyme Therapeutics, Inc. \$97,220 direct/yr 1  
 Self-Amplifying Plasmids That Kill Cancer Cells \$194,307 Total direct/yr 1-2  
 The major goal of this project is to study a combination of tumor selective amplification and gene expression to facilitate efficient and specific killing of tumor cells.

P50 CA 112970 (Korn) (Co-Investigator) 1/1/2005 – 12/31/2010  
 NIH/NCI \$268,853 direct/yr 1  
 UC/Lawrence Berkeley Lab Subcontract \$1,461,856 Total direct/yr 1-5  
 The major goal of this program is to develop and experimentally validate a computational model of Raf-MEK-ERK signaling in breast cancer that will predict individual responses to therapeutic agents that inhibit Raf-MEK-ERK signaling.

BIO07-10642-UC (PI) 2/1/2008 - 1/31/2010  
 UC Discovery-Biotechnology \$118,633 direct/yr 1  
 Self-Amplifying Plasmids That Kill Cancer Cells \$243,576 Total direct/yr 1-2  
 The major goal of this project is to study a combination of tumor selective amplification and gene expression to facilitate efficient and specific killing of tumor cells.

P50 CA58207 Gray (Co-Investigator) 08/1/2002 - 11/30/2007  
 NIH/NCI \$694,138 direct/yr 8  
 Bay Area Breast Cancer Translational Research Program \$8,000,050 Total direct/yr 8-13  
 Project 2  
 Therapeutic Implications of Amplification of Receptor Tyrosine Kinase (RTK) Signaling Pathway Genes  
 In this program, we will attempt to understand the molecular basis of the variable response amongst breast cancer cells to targeted therapeutics, such as Herceptin and EGF-receptor inhibitors.

P30 CA82103 (PI) 08/05/1999 – 08/31/2007  
 NIH/NCI \$852,117 direct/yr 1  
 Cancer Center Support Grant \$29,343,177 direct/yr 1-8  
 The Cancer Center Support Grant provides support for administration and infrastructure for the UCSF Comprehensive Cancer Center. Dr. Frank McCormick is the Director of the Cancer Center.

Onyx Corp. (PI) 01/28/2003 – 01/27/2007  
 Replicating Viruses for Treating Cancer \$349,999.56 direct/yr 1  
 \$1,082,698.01 Total direct/yr 1-3  
 The research project shall consist of experiments aimed at identifying/construction novel replicating viruses and methods/compositions of using the same for treating cancer.

Daiichi Pharmaceuticals (PI) 07/01/2001 - 06/30/2004  
 Survival Pathways in Cancer Cells \$1,048,385 direct/yr 1  
 \$3,089,786 Total direct/yr 1-3  
 This program seeks to identify new targets for therapeutic intervention, based on signal transduction pathways that promote cancer cell survival. In collaboration with Daiichi, we will screen for drugs that block these pathways selectively.

Biostar02-10242 (PI) 01/28/2003-01/27/2006  
 UC Discovery Grant \$349,999.56 direct/yr 1  
 Replicating Viruses for Treating Cancer \$1,082,698.01 Total direct/yr 1-3  
 The goal of this project is to use molecular analysis of cancer cells infected with ONYX-015 to devise and test new strategies for improving efficacy of this promising new anti-cancer agent.

DAMD17-03-1-0170 (PI) 05/01/2003-05/31/2006  
 DOD Idea Award \$148,152 direct/yr 1  
 Identification of Functions of Neurofibromin Distinct from RasGAP Domain \$442,793 Total direct/yr 1-3  
 The goals of this project are to establish a system for blocking signals detected by neurofibromin and Ira proteins using yeast as a model organism; and to identify the nature of the signals using genetic, biochemical and genomic approaches.

Biostar02-10331 Gray (Co-Investigator) 08/19/2003-08/18/2006  
 UC Discovery Grant \$100,000 direct/yr 1  
 Validating Breast Cancer Therapeutic Targets \$300,000 Total direct/yr 1-3  
 The overall goal of this project is to identify and validate new therapeutic targets in breast cancer and to identify candidate therapeutic agents against these targets.

Pilot Studies Award (PI) 10/01/2003-09/30/2004  
 National Neurofibromatosis Foundation \$25,000 direct/yr 1  
 A Screen for IRA/Neurofibromin Functions Distinct from the GAP Domain \$25,000 Total direct/yr 1  
 Major goals: *Saccharomyces cerevisiae* has two neurofibromin homologs, Ira1 and Ira2, whose functions can be complemented by the human protein, and whose homology with neurofibromin extends across most of the protein, including sequences flanking the GAP domain. We propose to study the functions of these flanking sequences using the power of yeast genetics and expression arrays.

#### **PEER REVIEWED PUBLICATIONS:**

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16. Innis, M. A., and **McCormick, F.**, 1986. Procedures for expression, modification, and analysis of human fibroblast interferon (IFN-beta) genes in heterologous cells. *Methods Enzymol* 119:397-403.
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## **NON-PEER REVIEWED PUBLICATIONS AND OTHER CREATIVE ACTIVITIES:**

### **Books and Chapters:**

#### **Book Chapters**

1. *25 Years of P53 Research* Editors: Hainaut, P; Wiman, K, 2007.
2. *The Molecular Basis of Cancer* Contributors: Mendelsohn, J; Israel, M; Howley, P; Gray, JW; Thompson, CB, 2008.
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#### **Edited Books:**

1. *Origins of Human Cancer*, Editors: Brugge J, Curran T, Harlow E, **McCormick F**, 1991.
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4. *The GTPase Superfamily*, Chairman: **McCormick F**, 1993.
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6. *Protein Tyrosine Kinases*, Editors: Fabbro D, **McCormick F**, 2006.

## **PATENTS ISSUED OR PENDING (ALLOWED)**

### **Issued Patents:**

1. U.S. Patent No. **4,762,706** Peptide antibodies and their use in detecting oncogene products – 8/9/1988
2. U.S. Patent No. **4,798,787** Peptide antibodies and their use in detecting oncogene products – 1/17/1989
3. U.S. Patent No. **4,966,843** Expression of interferon genes in Chinese hamster ovary cells – 10/30/1990
4. U.S. Patent No. **5,057,410** Chimeric messenger RNA detection methods – 10/15/1991
5. U.S. Patent No. **5,104,975** Compositions for detecting ras gene proteins and cancer therapeutics – 4/14/1992
6. U.S. Patent No. **5,234,839** Compositions for detecting ras gene proteins and cancer therapeutics – 8/10/1993
7. U.S. Patent No. **5,376,567** Expression of interferon genes in Chinese hamster ovary cells – 12/27/1994
8. U.S. Patent No. **RE35,171** Compositions for detecting ras gene proteins and cancer therapeutics – 3/5/1996
9. U.S. Patent No. **5,610,276** Polypeptides and antibodies derived from GAP associated protein, p62 – 3/11/1997
10. U.S. Patent No. **5,635,399** Retroviral vectors expressing cytokines – 6/3/1997

11. U.S. Patent No. **5,652,130** Retroviral vectors expressing tumor necrosis factor (TNF) – 7/29/1997
12. U.S. Patent No. **5,677,178** Cytopathic viruses for therapy and prophylaxis of neoplasia – 10/14/1997
13. U.S. Patent No. **5,731,427** Nucleic acids encoding a gap-associated protein – 3/24/1998
14. U.S. Patent No. **5,760,203** Gap gene sequences – 6/2/1998
15. U.S. Patent No. **5,763,573** GTPase activating protein fragments – 6/9/1998
16. U.S. Patent No. **5,773,237** Method for determining tyrosine kinase activity – 6/30/1998
17. US. Patent No. **5,801,029** Cytopathic viruses for therapy and prophylaxis of neoplasia – 9/1/1998
18. U.S. Patent No. **5,846,945** Cytopathic viruses for therapy and prophylaxis of neoplasia – 12/8/1998
19. U.S. Patent No. **5,856,181** Cytopathic viruses for therapy and prophylaxis of neoplasia – 1/5/1999
20. U.S. Patent No. **5,972,706** Cytopathic viruses for therapy and prophylaxis of neoplasia – 10/26/1999
21. U.S. Patent No. **6,617,496** Effecting virus resistance in plants through the use of negative strand RNAs – 9/9/2003
22. U.S. Patent No. **6,787,321** Mammalian two-hybrid system for screening for modulators of the accumulation of metabolic products – 9/7/2004
23. U.S. Patent No. **7,358,086** Mammalian two-hybrid system for screening for modulators of the accumulation of metabolic products – 4/15/2008

#### OTHER CREATIVE ACTIVITIES:

Melanoma Therapeutics Foundation Website Portal

<http://melanomatherapeutics.org/index.html>

UCSF/Halozyme Therapeutics, Inc. Sharepoint Collaboration Website

<https://cc-sharepoint.ucsf.edu/mccormick/biostar/default.aspx>

ProteinPlanet, Inc.

[www.proteinplanet.com](http://www.proteinplanet.com)

#### ABSTRACTS

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|------|---|
| 1991 | <b>McCormick, F.</b> "The Success And Failure Of Targeted Therapies." International Melanoma Congress.  |
| 1997 | <b>McCormick, F.</b> and Kirn, D. "Adenovirus Mutants with Host Ranges Restricted To Tumor Cells."  |
| 1997 | <b>McCormick, F.</b> "Cancer Therapies Based On Ras And P53 Mutations."   |
| 1998 | Tetsu, O., Korn, M. and <b>McCormick, F.</b> "Regulation of Cyclin D1 and P53 in Colon Cancer Cells" Switzerland.                                   |
| 1999 | <b>McCormick, F.</b> "Altered Signaling Pathways In Colon Cancer Cells."  |
| 1999 | <b>McCormick, F.</b> "Tumor Therapy with Modified Adenoviruses."  |
| 2000 | <b>McCormick, F.</b> "Cancer Therapy Based On the P53 Pathway."   |
| 2000 | <b>McCormick, F.</b> "Interactions between Ras, Beta-Catenin and P53 Pathways in Human Cancer" Madrid, Spain.                                       |
| 2000 | <b>McCormick, F.</b> "Interactions Between Ras, beta-catenin and p53 Pathways in Human Cancer." 11 <sup>th</sup> Annual Pezcoller Symposium, Italy. |
| 2000 | <b>McCormick, F.</b> "Cancer Therapy Based on P53."   |



- 2000 **McCormick, F.**, Kirn, D., Heise, K., Sampson-Johannes, A. "ONYX 015: A Potential Oncolytic Virus Specific for p53-Deficient Tumors." AACR Special Conference, Vail, Colorado.
- 2000 **McCormick, F.** "Adenoviruses with Host Ranges Restricted To Cancer Cells." Berlin, Germany.
- 2000 **McCormick, F.** "Cancer Therapies based on Ras and p53." Stanford, California.
- 2000 **McCormick, F.**, O'Shea, C., Shen, J. and Johnson, L. "Virus That Replicate Selectively In Cancer Cells."
- 2002 **McCormick, F.** "Adenoviruses Selective for Cancer Cells Based on the RB and P53 Pathways."
- 2002 **McCormick, F.** "Cancer Therapy Based On Ras And Related Proteins." World Congress of Pharmacology, San Francisco, California.
- 2003 **McCormick, F.** "Cancer Therapy Based on Ras and P53 Pathways." Japan Society of Clinical Oncology, Sapporo, Japan.
- 2004 **McCormick, F.**, Tetsu, O., Korn, M. and O'Shea, C. "Cancer Therapy Based on Ras and P53 Pathways." Case Western, Cleveland, Ohio.
- 2004 **McCormick, F.**, Tetsu, O., Korn, M. and O'Shea, C. "The Ras Pathway." University of New Mexico, CMDP Seminar, Albuquerque, New Mexico.
- 2005 **McCormick, F.** "New Targets in The Ras Pathway."
- 2005 **McCormick, F.** "The New Era of Targeted Cancer Therapy." Singapore.
- 2005 **McCormick, F.** "Cancer Therapy Based On the Ras Pathway." Singapore.
- 2005 **McCormick, F.** "New targets in the Ras pathway."
- 2006 **McCormick, F.** "Novel Regulators and Effectors of the Ras Pathway."
- 2006 **McCormick, F.** "Drug Targets in the Ras Pathway." Beatson Conference, Glasgow, Scotland, U.K.
- 2006 **McCormick, F.** "New Targets." Bay City Capital CEO Conference Cancer Symposium, Phoenix, AZ.
- 2006 **McCormick, F.** "The Ras Pathway in Cancer." 2006 Annual AACR Meeting, Washington, DC.
- 2006 **McCormick, F.** "The Success and Failure of Targeted Therapies." Stanford Medical School Cancer Biology Retreat Conference, Asilomar, CA.
- 2007 **McCormick, F.** "Mutation Detection Strategies for Diagnostics." 2007 AACR Annual Meeting, Los Angeles, CA.
- 2007 **McCormick, F.** "Drug Targets in the Ras Pathway." 1<sup>st</sup> International Costello Syndrome Research Symposium, Portland, OR.
- 2007 **McCormick, F.** "The Success and Failure of Targeted Therapies." 2007 International Melanoma Congress, New York, NY.
- 2007 **McCormick, F.** "Targeting the Ras Pathway." CNIO (Centro Nacional de Investigaciones Oncologicas) Conference, Madrid, Spain.
- 2007 **McCormick, F.** "Future Prospects For Targeted Therapies." NCRI (National Cancer Research Institute) Conference, Birmingham, U.K.
- 2008 **McCormick, F.** "Targeting the Ras Pathway." 19<sup>th</sup> Annual Cancer Progress Conference, New York, NY.

## RESEARCH PROGRAM:

### Significant Recent Publications

1. O'Shea, C., Johnson, L., Bagus, B., Choi, S., Nicholas, C., Shen, A., Boyle, L., Pandey, K., Soria, C., Kunich, J., Shen, Y., Habets, G., Ginzinger, D., **McCormick, F.** 2004. Late viral RNA export, rather than p53 inactivation, determines ONYX-015 tumor selectivity. *Cancer Cell* 6: 611-23.

Nature of Contribution: I supervised Dr. O'Shea, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

2. Macrae M., Neve R.M., Rodriguez-Viciana P., Haqq C., Yeh J., Chen C., Gray J.W., **McCormick F.** 2005. A conditional feedback loop regulates Ras activity through EphA2. *Cancer Cell* 8: 111-8.

Nature of Contribution: I supervised Dr. Macrae, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

3. Rodriguez-Viciana, P., Oses-Prieto, J., Burlingame, A., Fried, M., **McCormick, F.** 2006. A phosphate holoenzyme comprised of shoc2/sur8 and the catalytic subunit of pp1 functions as an M-Ras effector to modulate Raf activity. *Molecular Cell* 22:217-30.

Nature of Contribution: I supervised Dr. Rodriguez-Viciana, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

4. Lee, S.H., **McCormick, F.** 2006. p97/DAP5 is a ribosome-associated factor that facilitates Protein synthesis and cell proliferation by modulating the synthesis of cell cycle proteins. *EMBO J* 25: 4008-19.

Nature of Contribution: I supervised Dr. Lee, a post-doctoral fellow in my lab, and played a major role in the writing of the paper.

5. Kitagawa, M., Lee, S.H., **McCormick, F.** 2008. Skp2 suppresses p53-dependent apoptosis by inhibiting p300. *Mol Cell* 29:217-31.

Nature of Contribution: I supervised Dr. Lee & M. Kitagawa, a post-doctoral fellow & student in my lab, and played a major role in the writing of the paper.

## RESEARCH PROGRAM SUMMARY

My research is focused on signal transduction pathways in cancer cells and ways of treating cancer based on these pathways. The Ras pathway has been my primary interest, although we are also interested in metabolic differences between cancer cells and normal cells, as well as defects in cancer proteins related to mitotic checkpoints. My lab is attempting to understand how oncogenic Ras alters cell growth and survival in cancer cells and in cells from patients suffering from neurofibromatosis. The latter disease is caused by loss of a negative regulator of Ras of the Ras GAP family, a family of enzymes that was discovered in my lab. Loss of the neurofibromin protein leads to hyperactivation of Ras in cells of neural crest origin: as a result patients expressing defective neurofibromin suffer from learning defects, multiple benign lesions and an increased risk of certain cancers. We are using a combination of yeast genetics and biochemistry to understand more about the function of neurofibromin and how it is regulated, as well as new ways of treating this terrible disease.

The Ras pathway is negatively regulated by intrinsic pathways that are not well understood, including those involving ephrins and sprout proteins. We are using biochemical methods to elucidate these pathways at the molecular level and hope that this will lead to new ways of blocking Ras activity for therapeutic purposes.

My lab has worked extensively on viruses that kill cancer cells selectively. We are developing this concept using self-amplifying plasmids that replicate in cancer cells specifically, and encode proteins that kill neighboring cancer cells. Plasmid amplification is driven by DNA replication proteins coded by the plasmid itself, and an origin of DNA replication also encoded in the plasmid. The replication protein has been modified to prevent amplification in normal cells, in which RB and p53 block activity.

## **EXHIBIT B**

## ARTICLES

# Heterochromatin silencing of p53 target genes by a small viral protein

Conrado Soria<sup>1\*</sup>, Fanny E. Estermann<sup>1\*</sup>, Kristen C. Espantman<sup>1</sup> & Clodagh C. O'Shea<sup>1</sup>

The transcription factor p53 (also known as TP53) guards against tumour and virus replication and is inactivated in almost all cancers. p53-activated transcription of target genes is thought to be synonymous with the stabilization of p53 in response to oncogenes and DNA damage. During adenovirus replication, the degradation of p53 by E1B-55k is considered essential for p53 inactivation, and is the basis for p53-selective viral cancer therapies. Here we reveal a dominant epigenetic mechanism that silences p53-activated transcription, irrespective of p53 phosphorylation and stabilization. We show that another adenoviral protein, E4-ORF3, inactivates p53 independently of E1B-55k by forming a nuclear structure that induces *de novo* H3K9me3 heterochromatin formation at p53 target promoters, preventing p53–DNA binding. This suppressive nuclear web is highly selective in silencing p53 promoters and operates in the backdrop of global transcriptional changes that drive oncogenic replication. These findings are important for understanding how high levels of wild-type p53 might also be inactivated in cancer as well as the mechanisms that induce aberrant epigenetic silencing of tumour-suppressor loci. Our study changes the longstanding definition of how p53 is inactivated in adenovirus infection and provides key insights that could enable the development of true p53-selective oncolytic viral therapies.

Tumour mutations and DNA virus proteins converge in inactivating p53 (ref. 1), which was initially discovered as a cellular target of SV40 Large T<sup>2,3</sup>. However, despite 30 years of research, the critical factors that determine p53-activated transcription are still not fully understood<sup>4,5</sup>. p53 is expressed constitutively in normal cells where its activity is limited by p53 protein degradation<sup>6</sup>. p53 activation is triggered in response to oncogenes and DNA damage, which stabilize p53 (refs 7–9). This has led to the general belief that the induction of p53 levels and phosphorylation<sup>10</sup> is synonymous with p53-activated transcription. As such, the induction of p53 levels is a standard read-out for p53 activation and rationale for several cancer therapies, including irradiation and genotoxic drugs<sup>11</sup>, MDM2 antagonists<sup>12</sup>, and the E1B-55k-deleted oncolytic adenoviral therapy, ONYX-015 (ref. 13).

The adenoviral protein, E1B-55k, binds to the p53 transactivation domain and is sufficient to inactivate p53 in cellular transformation<sup>7,14</sup>. In infection, E1B-55k forms a complex with another adenoviral protein, E4-ORF6, which recruits a cellular ubiquitin ligase that targets p53 for degradation<sup>15,16</sup>. The degradation of p53 by E1B-55k is thought to be the critical event that inactivates p53 for virus replication<sup>17</sup>. An E1B-55k-deleted virus<sup>18</sup>, dl1520/ONYX-015, induces high p53 levels, which was expected to limit viral replication in normal cells but not p53 mutant tumour cells<sup>13</sup>. On this basis, ONYX-015 (ref. 13) was tested in patients as a p53 tumour-selective oncolytic viral therapy<sup>19,20</sup> and is now approved in several countries (known as Oncorine). However, the loss of E1B-55k functions in viral RNA export, rather than p53 inactivation, is the major determinant of  $\Delta$ E1B-55k tumour selectivity<sup>21,22</sup>. Contrary to expectations, although p53 accumulates to high levels in the nucleus of  $\Delta$ E1B-55k ( $\Delta$ 55k)-infected human primary small airway epithelial cells (SAECs), the physiological target cells for adenovirus infection, p53 transcriptional targets, such as *p21* (also known as *CDKN1*), *MDM2*, *CCNG*, *14-3-3 $\sigma$*  (also known as *SFN*), *PERP*, *PIG3* (also known as *TP53I3*) and *GADD45*, are not induced (Fig. 1a and ref. 21). The

failure of p53 stabilization to activate transcriptional targets is not a tissue-specific effect and occurs in multiple primary cell types and tumour cell lines (Supplementary Figs 1–3), including U2OS tumour cells where p53 targets are suppressed to a similar extent as that in cell-lines with p53 mutations. This reveals a fundamental gap in our understanding of not only adenovirus biology but also p53 activation.

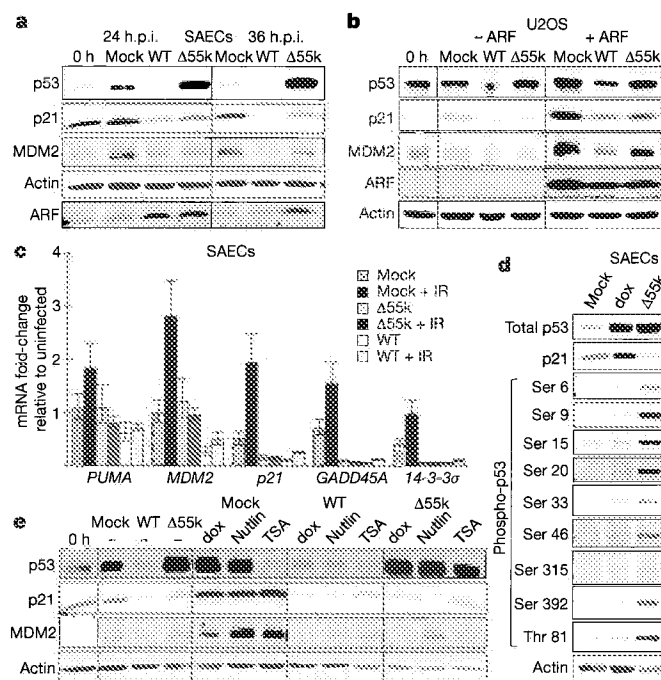
## p53 stabilization without activity

Cellular and viral oncogenes, such as *Ras* and adenovirus *E1A*, trigger p53 activation by inducing the expression of ARF<sup>9</sup>, which inhibits MDM2-mediated p53 degradation. ARF is lost in 58% of cancers<sup>9</sup>, which had previously been invoked as the critical factor that prevents p53 activation in  $\Delta$ E1B-55k-infected tumour cells<sup>23</sup>. Using a U2OS stable cell-line (p53 wild-type, ARF negative) in which ARF expression is induced by isopropyl- $\beta$ -D-thiogalactopyranoside (IPTG), we show that ARF stabilizes p53 and activates p21 transcription in mock infection. Nevertheless, although ARF expression increases basal p53 activity, the induction of p21 is repressed in both wild-type- and  $\Delta$ E1B-55k-infected cells (Fig. 1b and Supplementary Fig. 4). Furthermore, endogenous ARF induction also fails to activate p53 targets in  $\Delta$ E1B-55k-infected SAECs (Fig. 1a). Thus, p53 is inactivated, irrespective of E1B-55k and ARF expression in adenovirus-infected cells.

DNA damage signals also have a critical role in activating p53, triggering p53 phosphorylation and protein stabilization<sup>8,24</sup>. In clinical trials,  $\Delta$ E1B-55k (ONYX-015), was used in combination with genotoxic chemotherapies, such as 5-fluorouracil<sup>19,20</sup>. We reasoned that the induction of p53 levels alone may not be sufficient to activate p53 in infected cells, and that DNA damage is also required. However, 5-fluorouracil fails to activate p53 in  $\Delta$ E1B-55k-infected U2OS cells (Supplementary Fig. 5). The DNA damage checkpoint is deregulated in many tumour cells. Therefore, we also analysed  $\Delta$ E1B-55k-infected SAECs and show that p53 transcriptional targets cannot be activated by  $\gamma$  irradiation (Fig. 1c and Supplementary Fig. 6),

<sup>1</sup>Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, California 92037-1099, USA.

\*These authors contributed equally to this work.



**Figure 1 | p53 is induced and phosphorylated in  $\Delta$ E1B-55k infection but p53 activity is dominantly suppressed.** **a**, SAECs were infected and protein lysates analysed by immunoblotting. **b**, U2OS cells with inducible ARF were infected as indicated and analysed for p53 levels and activation by immunoblotting. **c**, RT-qPCR of p53 transcriptional targets in infected SAECs (36 h.p.i.)  $\pm$  10 Gy  $\gamma$  irradiation (IR). Error bars represent s.d. ( $n = 3$ ). **d**, Immunoblot of p53 protein phosphorylation in infected or doxorubicin (dox)-treated SAECs (36 h.p.i.). **e**, Immunoblot of SAECs (36 h.p.i.) infected as indicated and treated with either control (–), dox, nutlin, or TSA at 24 h.p.i.

ultraviolet irradiation (Supplementary Fig. 7) or doxorubicin (dox, Fig. 1e).

The activation of p53 in response to DNA damage is mediated via kinases, such as ATM, ATR, DNA-PKs (also known as PRKDC), CHK1 and CHK2, which phosphorylate p53 (ref. 8) at key residues, stabilizing p53 and potentiating p53–DNA binding<sup>24</sup>. A possible explanation for the failure of DNA damage to activate high p53 levels in  $\Delta$ E1B-55k-infected cells is that p53 phosphorylation is inhibited by viral infection. However, even without the introduction of exogenous genotoxic stress, p53 is already highly phosphorylated at multiple sites targeted by DNA damage kinases in  $\Delta$ E1B-55k-infected SAECs (Fig. 1d). Thus, although oncogenes and DNA damage trigger p53 stabilization and phosphorylation in  $\Delta$ E1B-55k-infected cells, p53 fails to activate the transcription of downstream effectors.

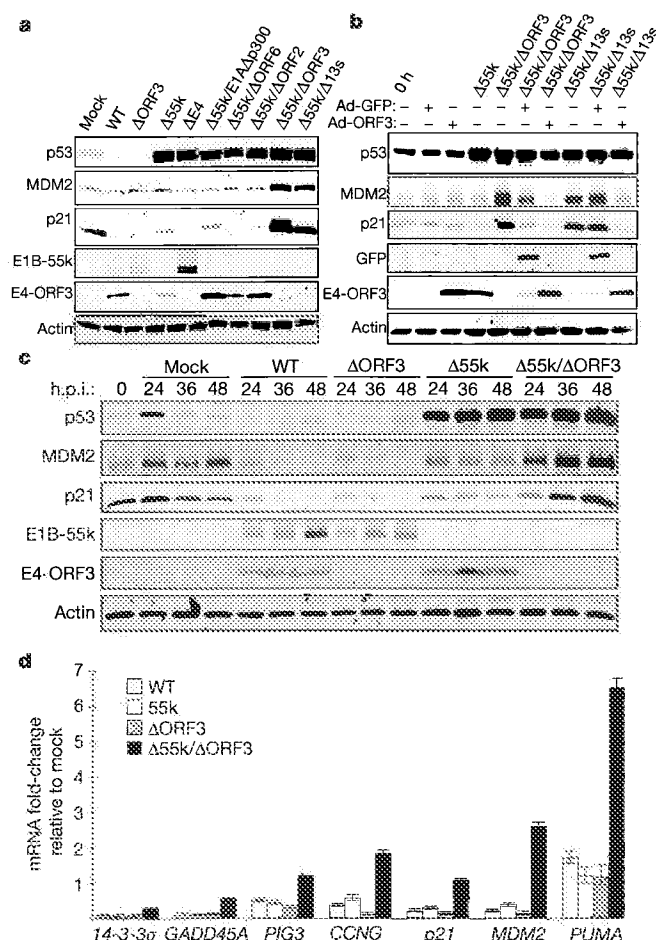
We next examined if, in the absence of E1B-55k, MDM2 binds and inactivates p53 in adenovirus-infected cells. Nutlin is a small molecule antagonist that inhibits MDM2–p53 binding<sup>12</sup>. In contrast to mock, nutlin fails to stabilize p53 further or induce p21 in  $\Delta$ E1B-55k-infected SAECs (Fig. 1e). The histone deacetylase (HDAC) inhibitor, trichostatin A (TSA), induces the expression of p21 independently of p53 stabilization or phosphorylation (Fig. 1e). However, in  $\Delta$ E1B-55k-infected cells, TSA fails to induce p21. We conclude that p53 transcriptional targets are dominantly suppressed in adenovirus-infected cells, irrespective of E1B-55k, and cannot be activated in response to radiation, genotoxic drugs, ARF, MDM2 antagonists or HDAC inhibitors.

#### E4-ORF3 inactivates p53 independently of E1B-55k

Our data strongly indicate that there is a previously undiscovered adenoviral protein that inactivates p53 independently of p53 degradation. To test this, we screened for p53 activation in primary cells infected with adenoviruses that have compound mutations in E1B-55k and other

early viral genes (Supplementary Fig. 8). In addition to deleting E1B-55k, the loss of either E1A-13s or E4-ORF3 is required to activate p53 in infected cells (Fig. 2a). This is surprising, especially because E1A is a potent oncogene that triggers p53 activation in cellular transformation<sup>7,14</sup>. In adenovirus infection, the E1A-13s splice form is required for the transactivation of other viral genes<sup>17</sup>, including E4-ORF3 (Fig. 2a). Consistent with this, we show that, in contrast to GFP (green fluorescent protein), the ectopic expression of E4-ORF3 rescues p53 inactivation in both  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3- and  $\Delta$ E1B-55k/ $\Delta$ E1A-13s-infected cells (Fig. 2b). The slight reduction of p21 by Ad-GFP in  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 co-infection is due to the partial activation of E4-ORF3 transcription (in *trans*) by E1A-13s, which does not occur in  $\Delta$ E1B-55k/ $\Delta$ E1A-13s co-infection (Supplementary Fig. 9). Hence, E1A-13s induces the expression of E4-ORF3, which then inactivates p53 via an E1B-55k-independent mechanism. Moreover, the expression of E4-ORF3 alone is also sufficient to inhibit p53 activation (Supplementary Fig. 10). These data reveal E4-ORF3 as a novel adenoviral protein that inactivates the p53 tumour-suppressor pathway.

The proposed p53 tumour selectivity of the  $\Delta$ E1B-55k oncolytic therapy, ONYX-015, is based on p53 stabilization being the sole critical event that determines p53-activated transcription. Although there is



**Figure 2 | E4-ORF3 inactivates p53 independently of E1B-55k and p53 degradation.** **a**, SAECs were infected with the indicated viruses (detailed description in Supplementary Fig. 8) and protein lysates (36 h.p.i.) were analysed for p53 activation by immunoblotting. **b**, SAECs were co-infected as indicated with either a GFP control virus (Ad-GFP, +) or a virus expressing E4-ORF3 (Ad-ORF3, +). Protein lysates (36 h.p.i.) were analysed for p53 activation by immunoblotting. **c**, SAECs were infected and harvested over a 48 h time course as indicated and analysed for p53 activation by immunoblotting. **d**, RT-qPCR of p53 transcriptional targets in infected SAECs at 36 h.p.i. Error bars represent s.d. ( $n = 3$ ).

some basal p53 activity in  $\Delta$ E1B-55k-infected cells compared to wild-type virus, the additional deletion of E4-ORF3 is necessary for p53 to activate downstream effectors over the course of infection (Fig. 2c, d). In contrast to p53 transcriptional targets, the mRNA levels of p53 and the housekeeping gene, *GUSB*, are not impacted by E4-ORF3 (Supplementary Fig. 11). p53 stabilization is required to activate p53 transcriptional targets, and does not occur in  $\Delta$ E4-ORF3 infection

where p53 is degraded by E1B-55k/E4-ORF6. Furthermore, using a p53-inducible stable cell-line (H1299-D1, Supplementary Fig. 12), we show that the induction of p21 and MDM2 in  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 infection is p53-dependent. Thus, the deletion of both E1B-55k and E4-ORF3 is necessary to activate p53 in adenovirus infection. We conclude that E4-ORF3 has a critical and novel role in inactivating p53 independently of E1B-55k and p53 degradation.

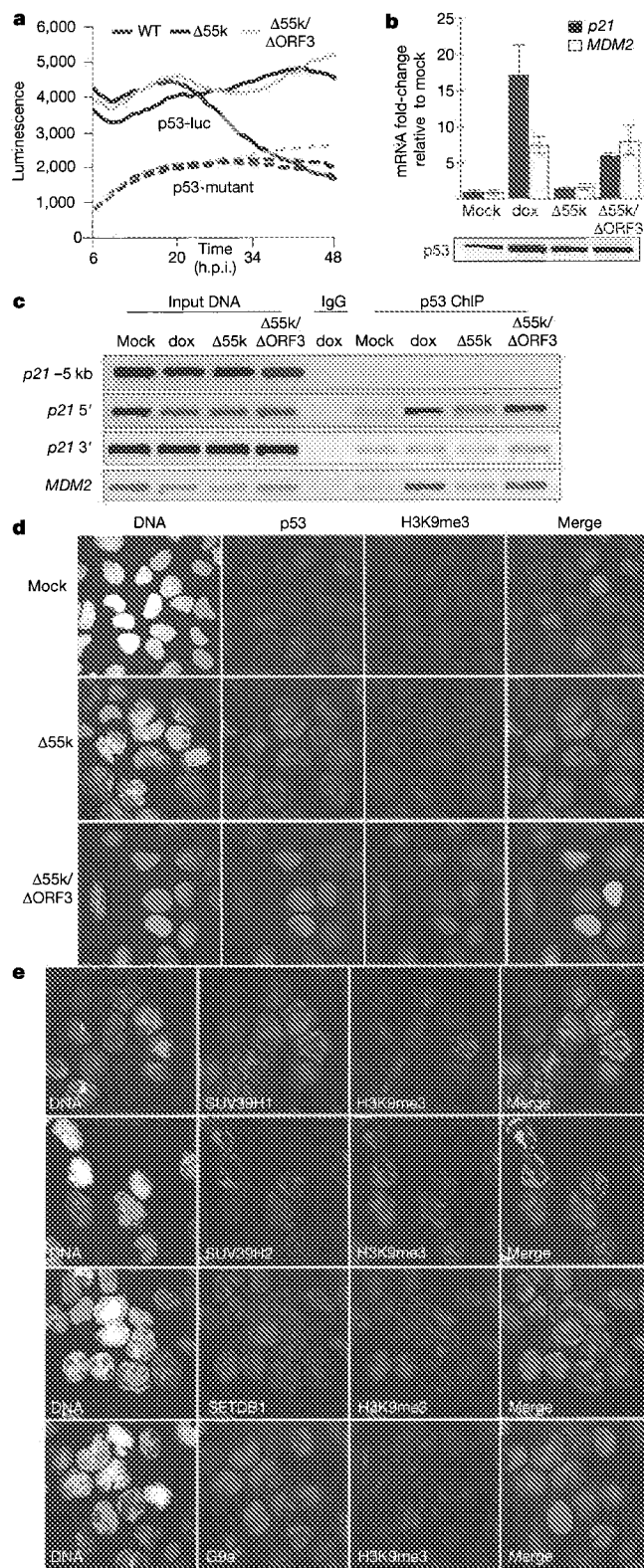
#### E4-ORF3 prevents p53-DNA binding at chromatin

DNA tumour virus proteins, such as E1B-55k, SV40 LT and HPV E6, inactivate p53 via direct high affinity protein-protein interactions<sup>1</sup>. However, contrary to this established paradigm, E4-ORF3 does not co-localize with p53 (Supplementary Fig. 13) or co-immunoprecipitate with p53 (data not shown). This indicates that E4-ORF3 inactivates p53 via a non-canonical mechanism.

The induction of p53 levels and phosphorylation induces p53 conformational changes that drive sequence-specific DNA binding and the recruitment of transcription co-factors<sup>25</sup>. A p53-DNA binding domain that is competent to bind to DNA can be distinguished by immunoprecipitation with monoclonal antibody PAB1620 versus PAB240 (ref. 26). p53 is immunoprecipitated selectively by PAB1620 in both  $\Delta$ E1B-55k- and  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3-infected cells (Supplementary Fig. 14), demonstrating that the p53 DNA-binding domain is in a protein conformation that should be capable of binding to DNA<sup>26</sup> in both cases. To determine functionally if E4-ORF3 prevents p53-DNA binding, we transfected U2OS cells with a p53 luciferase plasmid (p53-luc), where p53 binding to consensus DNA sequences activates luciferase transcription<sup>27</sup>. A control pGL3-luciferase reporter (non-p53 promoter) is activated to similar levels in all viral infections (Supplementary Fig. 15). In wild-type-virus-infected cells, p53-activated transcription of luciferase is inhibited after 24 h (Fig. 3a), which is expected due to p53 degradation. In contrast, p53-luciferase is activated in both  $\Delta$ E1B-55k and  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 infection (Fig. 3a). The induction of luciferase requires p53-DNA binding, since a mutated p53 response element (p53-mutant) abolishes luciferase activity. These experiments demonstrate that E4-ORF3 does not compete with p53 for binding to consensus DNA target sequences or prevent p53 transcriptional activation of promoters in ectopic reporter plasmids.

The ability of E4-ORF3 to prevent p53-activated transcription of endogenous targets, but not ectopic p53-luciferase plasmids, is at first difficult to reconcile. Plasmid DNA is not subject to the same architectural and packing constraints as DNA in cellular chromatin. Therefore, we performed p53 chromatin immunoprecipitations (ChIPs) to determine if E4-ORF3 specifically prevents p53-DNA binding in the context of cellular chromatin. p53 binding to target sites in the *p21* (5' and 3' site) and *MDM2* promoters<sup>25</sup> is induced upon doxorubicin treatment and  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 infection, where it activates the transcription of *p21* and *MDM2* RNAs (Fig. 3b, c). In contrast, although p53 is induced to similar levels, E4-ORF3 prevents p53-DNA binding to the *p21* and *MDM2* promoters in  $\Delta$ E1B-55k-infected cells (Fig. 3b, c and Supplementary Fig. 16). Thus, E4-ORF3 inactivates p53 by preventing p53 binding to DNA target sites specifically in the context of cellular chromatin.

**Figure 3 | E4-ORF3 induces heterochromatin formation and prevents p53-DNA binding at endogenous promoters.** **a**, U2OS cells were transfected with p53-luc (solid line) or p53-mutant (dashed line) luciferase plasmids and infected with indicated viruses. Luminescence is plotted against time. **b**, **c**, U2OS cells were infected as indicated or treated with doxorubicin. **b**, p53 induction was analysed by immunoblotting and p53 transcriptional targets quantified by RT-qPCR (36 h.p.i.). Error bars represent s.d. ( $n \geq 3$ ). **c**, p53 ChIPs were analysed by semiquantitative PCR for *p21* and *MDM2* promoter sequences. **d**, p53 (green) and H3K9me3 (red) immunofluorescence of infected U2OS cells (36 h.p.i.). **e**, Localization of SUV39H1, SUV39H2, SETDB1 and G9a (green) with H3K9me3 (red) in  $\Delta$ 55k-infected U2OS cells (36 h.p.i.).



### Repressive histone methylation silences p53 targets

We reasoned that p53–DNA binding depends not only on the protein conformation of p53 but also the accessibility of target promoters in the cellular genome. We proposed that E4-ORF3 could inactivate p53 by inducing heterochromatin at endogenous target promoters, preventing the access of p53 to DNA. Heterochromatin compaction is specified by the loss of histone acetylation and induction of repressive histone methylation<sup>28</sup>. TSA fails to induce p21 in  $\Delta$ E1B-55k-infected SAECs (Fig. 1e), indicating that E4-ORF3 inactivates p53 targets via a mechanism that is dominant to the inhibition of histone deacetylation. In cancer, the aberrant epigenetic silencing of tumour-suppressor genes, such as *p16<sup>INK4a</sup>* (also known as *CDKN2A*), is initiated by the methylation of histone H3 at lysine 9 (H3K9)<sup>29</sup>. p53 localization is indistinguishable in  $\Delta$ E1B-55k- and  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3-infected cells (Fig. 3d). However, in  $\Delta$ E1B-55k-infected cells, where p53 is inactive, dense regions of H3K9me3 repressive heterochromatin are induced at the periphery of the nucleus (Fig. 3d and Supplementary Fig. 17). Of the four known methyltransferases that catalyse H3K9 trimethylation (H3K9me3), we show that SUV39H1 and SUV39H2 (which share 59% sequence identity and have redundant functions)<sup>30,31</sup>, but not SETDB1 (ref. 32) or G9a (also known as EHMT2, ref. 33), are specifically associated with the formation of *de novo* H3K9me3 heterochromatin domains in  $\Delta$ E1B-55k-infected nuclei (Fig. 3e). The formation of these domains requires E4-ORF3 and does not occur in either mock- or  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3-infected cells (Supplementary Figs 18–21).

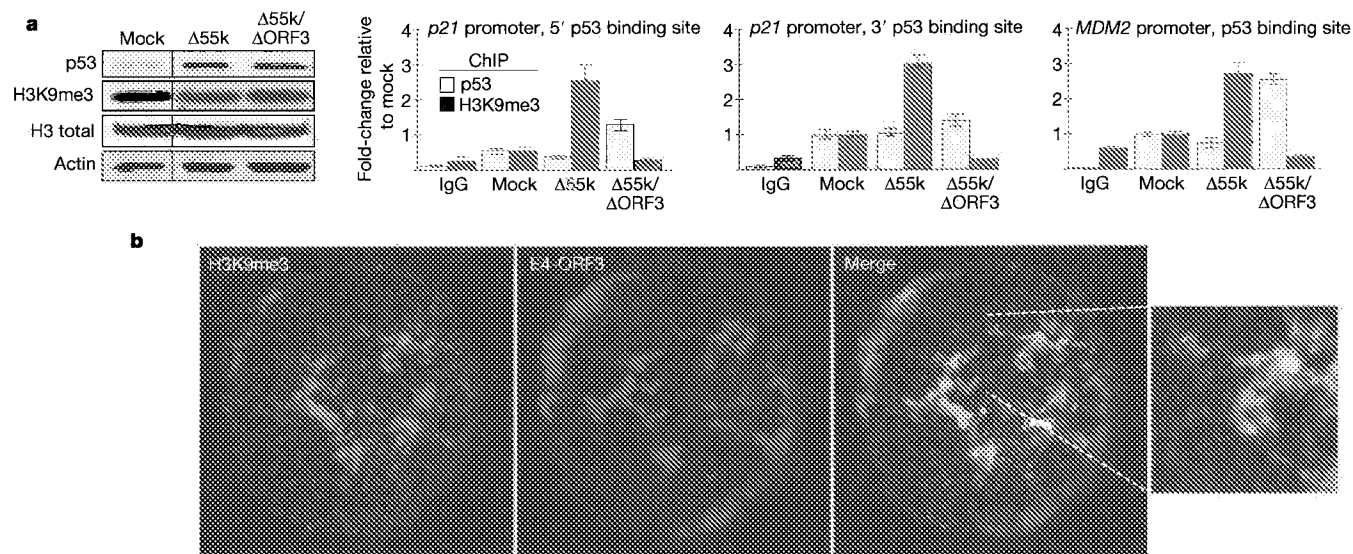
These data demonstrate that E4-ORF3 induces novel H3K9me3 heterochromatin, which could deny p53 access to endogenous target promoters. To test this, we performed p53 and H3K9me3 ChIPs. The induction of repressive heterochromatin by E4-ORF3 is not associated with a global upregulation of either total histone H3 or H3K9me3, which are at similar levels in all infections (Fig. 4a). In  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3-infected cells, p53 binding is induced at *p21* and *MDM2* promoter sites (consistent with Fig. 3c), whereas H3K9me3 is at a similar level to an IgG-negative control (Fig. 4a and Supplementary Fig. 22). In contrast, in  $\Delta$ E1B-55k-infected cells, H3K9me3 is enriched at the *p21* and *MDM2* promoters where p53 binding is prevented. H3K9me3 is also induced at the –5 kb region of the *p21* promoter and is not restricted to p53 binding sites (Supplementary Fig. 22). Thus, in cells expressing E4-ORF3, there

is an inverse correlation between p53 and H3K9me3 at p53-regulated promoters. The same conclusions were reached for additional p53 targets, including *GADD45A*, *FAS*, *PUMA* (also known as *BBC3*) and *PIG3* (Supplementary Figs 22–24). In contrast, at non-p53-regulated promoters, such as *ACTIN* (also known as *ACTA*) and *POLR2*, H3K9me3 is not induced in  $\Delta$ E1B-55k-infected cells relative to mock (Supplementary Figs 22 and 24). Basal H3K9me3 is decreased at these promoters in  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3-infected cells, indicating that E4-ORF3 may also restrain global demethylase activity. We conclude that E4-ORF3 inactivates p53 by inducing *de novo* H3K9me3 heterochromatin silencing at p53 target promoters. With access denied, p53 is powerless to activate the transcription of downstream effectors.

The induction of heterochromatin formation is still relatively poorly understood. Thus, a major question is how is E4-ORF3 directly involved in inducing repressive H3K9me3 heterochromatin at p53 target promoters? E4-ORF3 does not co-localize with p53 and forms a distinctive web-like structure in the nucleus (Supplementary Fig. 13). We show that E4-ORF3 demarcates the formation of *de novo* H3K9me3 heterochromatin domains in  $\Delta$ E1B-55k-infected cells. E4-ORF3 is, for the most part, adjacent to H3K9me3, indicating it acts as a novel platform that catalyses heterochromatin formation through transient or long-range interactions (Supplementary Figs 25–27). Using high-resolution confocal microscopy, we show that E4-ORF3 forms a continuous scaffold that specifies *de novo* heterochromatin assembly as it weaves through the nucleus (Fig. 4b). These data demonstrate a direct role for E4-ORF3 in orchestrating H3K9me3 heterochromatin silencing at p53 target promoters. Furthermore, they reveal an extraordinary nuclear scaffold that either builds on existing architectural features that organize cellular DNA or is a novel viral construction that targets heterochromatin assembly at p53 target promoters.

### Selective silencing of the p53 transcription program

These data beg the question as to the specificity of E4-ORF3 in silencing p53 targets. To determine the global consequences on cellular transcription, we performed genome-wide expression analyses on infected SAECs (Supplementary Figs 28 and 29). These studies demonstrate that E4-ORF3 is an exclusive player in the global transcriptional changes induced upon viral infection. There are 1,730 overlapping genes that are similarly up or downregulated by a log-fold change



**Figure 4 | E4-ORF3 forms a nuclear scaffold that specifies heterochromatin assembly and H3K9 trimethylation at p53 target promoters.** **a**, Protein lysates from infected U2OS cells (36 h.p.i.) were analysed for total histone H3 or H3K9me3 levels by immunoblotting. H3K9me3 and p53 ChIPs were quantified by RT-qPCR, normalized relative to input DNA and plotted as fold-change relative to mock. Error bars

represent s.d. ( $n = 2$ ). **b**, H3K9me3 (green) and E4-ORF3 (red) localization in  $\Delta$ 55k-infected SAECs (36 h.p.i.) was visualized by immunofluorescence. A high resolution confocal slice (0.3  $\mu$ m) through the nucleus is shown with a magnified section of E4-ORF3 and associated heterochromatin domains on the far right.

greater than two in both  $\Delta$ E1B-55k and  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 versus mock, which reflect a common transcriptional program (Fig. 5a). These global changes are associated with the cell cycle and E2F activation (Supplementary Tables 1 and 2). This is consistent with E1A-mediated inactivation of RB<sup>34</sup> and recruitment of p300 and PCAF (also known as EP300 and KAT2B, respectively) to induce active histone acetylation marks at the promoters of genes involved in cell growth, division and DNA synthesis<sup>35,36</sup>. Thus, E4-ORF3-induced heterochromatin silencing, as well as the scaffold it forms throughout the nucleus, does not affect the global activation of cellular transcripts induced by viral infection.

To define the genes specifically targeted by E4-ORF3, we compared  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3- versus  $\Delta$ E1B-55k-infected cells. E4-ORF3 prevents the transcriptional activation of 265 genes by a log-fold change of two or more in  $\Delta$ E1B-55k-infected cells. To determine how many of these genes are likely to be regulated by p53, we used two criteria: the presence of consensus p53-DNA binding sites in their promoters and their induction upon treatment with the MDM2 antagonist, nutlin. A heat map of top transcripts differentially upregulated in response to  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 and nutlin includes well known p53 targets (*MDM2*, *FAS*, *PIG3*, *TP53INP1*, *BTG2*, *LRDD*) associated with

growth inhibition and apoptosis, as well as novel targets (*HRH1*, *RNASE7*, *JMJD1C*) (Fig. 5b and Supplementary Fig. 30). Of the 265 differentially upregulated genes, 73% are induced in response to nutlin and/or have predicted p53 binding sites (Fig. 5c and Supplementary Tables 3, 4). A pathway analysis of E4-ORF3-regulated transcripts indicates that, in addition to the p53 pathway, there is a significant over-representation of genes associated with immune modulation as well as tissue/vascular remodelling (Supplementary Table 5). These data indicate that E4-ORF3 may target p53 promoters as part of a general anti-viral transcriptional silencing program, which is consistent with the highly defective replication of  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 in primary cells (Supplementary Fig. 31).

## Discussion and perspective

The conclusions of our study challenge the general assumption that p53 induction and phosphorylation is tantamount to p53 activity, which is the premise for several cancer therapies<sup>11–13</sup>. Our data reveal a novel and dominant mechanism of p53 inactivation that acts through the targeted epigenetic silencing of p53 target promoters. We identify a viral protein, E4-ORF3, which seems to form a novel scaffold that weaves through the nucleus, directing SUV39H1/2 H3K9me3 heterochromatin assembly at p53 target promoters to silence p53-activated transcription in response to genotoxic and oncogenic stress (Fig. 5d). Remarkably, this suppressive nuclear web selectively ensnares p53 and anti-viral genes while operating in the backdrop of global transcriptional changes that drive pathological cellular and viral replication.

There is a profound functional overlap between adenovirus early proteins and tumour mutations<sup>37</sup>. Thus, a major question is if E4-ORF3 reflects or exerts an existing cellular mechanism and nuclear structure that censors p53 transcriptional activity. Strikingly, all of the known targets of E4-ORF3, PML<sup>38</sup>, the MRE11/RAD50/NBS1 (NBS1 is also known as NBN) (MRN) DNA damage/repair complex<sup>39</sup> and Tifl $\alpha$ <sup>40</sup> (also known as TRIM24) are subverted by tumour mutations. It is intriguing to speculate that E4-ORF3 physically integrates the inhibitory effects of several cancer pathway mutations, both known and yet to be discovered, which together have emergent functions<sup>4</sup> in silencing p53 activity. Similar to the discovery of p53 with a viral protein<sup>2,3</sup>, E4-ORF3 provides a powerful dynamic probe with which to define critical cellular factors that induce *de novo* epigenetic silencing of p53 target promoters in somatic cells. This has important implications for understanding how high levels of wild-type p53 might also be inactivated in cancer as well as the dynamic mechanisms that induce aberrant epigenetic silencing of tumour-suppressor gene loci. Finally, our identification of E4-ORF3 changes the fundamental definition of how p53 is inactivated in adenovirus-infected cells, which is a critical mechanistic insight that could now enable the rational development of true p53 tumour-selective adenoviral therapies.

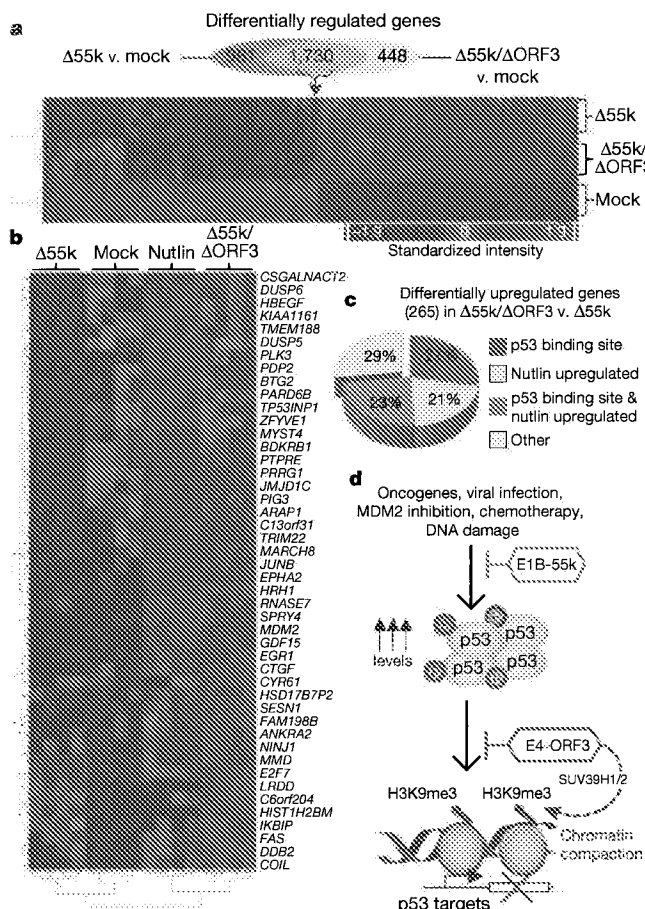
## METHODS SUMMARY

Cells were grown and infected with established conditions<sup>21,22</sup>. Protein lysates were analysed by western blotting<sup>21,22</sup>. Quantitative polymerase chain reaction with reverse transcription (RT-qPCR) was used to quantify p53 targets<sup>21</sup>, and normalized relative to 18S. For luciferase assays, U2OS cells were transfected and infected after 36 h. D-Luciferin (100  $\mu$ M) was added 4 h post-infection (h.p.i.) and luminescence quantified every hour. Global gene expression was determined using Affymetrix Human Exon 1.0ST arrays and analysed with Partek and Genomatrix software.

**Full Methods** and any associated references are available in the online version of the paper at [www.nature.com/nature](http://www.nature.com/nature).

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**Figure 5 | p53 transcriptional targets are silenced selectively in the backdrop of global transcriptional changes that drive oncogenic cellular and viral replication.** Affymetrix global gene expression analyses of SAECs. **a**, Heat map of the 1,730 overlapping differentially regulated genes (log-fold change  $>2$  or  $<-2$  with a false discovery rate (FDR) of 0.05) between  $\Delta$ 55k/ $\Delta$ ORF3- and  $\Delta$ 55k- versus mock-infected SAECs (36 h.p.i.). **b**, Unsupervised hierarchical clustering of 46 top differentially upregulated transcripts in both  $\Delta$ 55k/ $\Delta$ ORF3 infection and nutlin treatment. **c**, Pie-chart depicting the percentage of upregulated transcripts (log-fold change  $>2$  and FDR of 0.05) in  $\Delta$ 55k/ $\Delta$ ORF3 versus  $\Delta$ 55k that have predicted p53 transcription factor binding sites and/or induced by a log-fold change  $>1.5$  in response to nutlin. **d**, Summary and model.



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**Author Contributions** C.S. performed the p53 activation and virus studies, including immunoblotting, RT-qPCR and microarray experiments. F.E.E. performed all chromatin immunoprecipitation and immunofluorescence studies. K.C.E. performed the luciferase assays, E4-ORF3 sufficiency and complementation, and assisted C.S. with viral mutant studies. C.C.O. analysed the array data and wrote the paper with contributions from all authors. C.C.O. was responsible for the overall conceptual design and supervision of the studies.

**Author information** Microarray data are deposited in NCBI's Gene Expression Omnibus (GSE20607). Reprints and permissions information is available at [www.nature.com/reprints](http://www.nature.com/reprints). The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at [www.nature.com/nature](http://www.nature.com/nature). Correspondence and requests for materials should be addressed to C.C.O. ([oshea@salk.edu](mailto:oshea@salk.edu)).

## METHODS

**Cells, growth conditions and viral infections.** Primary human cells from multiple donors were obtained from Cambrex/Lonza, which were grown and infected as described previously<sup>21,22</sup>. Multiplicities of infection (m.o.i.) were determined experimentally. U2OS, H1299-D1, MDA-MB-231, HCT-116, C33A and A549 cells were infected at a m.o.i. of 30, and SAECs, HMEC and HBEC at a m.o.i. of 10. U2OS cells with an IPTG-inducible *ARF*<sup>21</sup> were a kind gift from G. Peter's laboratory. H1299-D1 is a stable cell line that expresses a p53 cDNA construct under the control of a ponasterone-inducible promoter. To induce p53 expression, cells were treated 5 h before infection with 5  $\mu$ M ponasterone A (Invitrogen), which was re-added at the time of infection.

**Viruses and viral replication assays.** Viral replication and titres were quantified by secondary infection of 293/E4/pIX cells using an ELISA assay with a rabbit anti-adenovirus type 5 antibody (Abcam) at 1:1,000, as described previously<sup>21,22,42</sup>. Mock infection was performed with the E1-deleted non-replicating adenovirus *dl*B12 (ref. 43). Wild-type virus is WtD<sup>18</sup>,  $\Delta$ E1B-55k ( $\Delta$ 55k) is *dl*1520/ONYX-015 (refs 13, 18). The  $\Delta$ E1B-55k/ $\Delta$ E4-ORF3 ( $\Delta$ 55k/ $\Delta$ ORF3) virus, *dl*B112, has an identical genome backbone to *dl*1520/ONYX-015 but has a single base pair deletion (nucleotide 7143r) that ablates E4-ORF3 expression<sup>44</sup>.  $\Delta$ E4 is *dl*B66 which has a deletion that ablates the E4 genes<sup>45</sup>.  $\Delta$ E1B-55k/ $\Delta$ E4-ORF6 ( $\Delta$ 55k/ $\Delta$ ORF6) is *dl*B67 which has mutations that ablate both E1B-55k and E4-ORF6 (ref. 46).  $\Delta$ ORF3 is E4inORF3 (ref. 47).  $\Delta$ E1B-55k/ $\Delta$ E1A-13s ( $\Delta$ 55k/ $\Delta$ 13s) has an E1B-55k gene deletion and mutation that ablates the 13s splice form of E1A<sup>48</sup>.  $\Delta$ E1B-55k/E1A $\Delta$ p300 ( $\Delta$ 55k/E1A $\Delta$ p300) has an E1B-55k deletion and E1A point mutation that abrogates E1A-p300 binding<sup>21,48</sup>. Ad-CMV E1-deleted replication-incompetent adenovirus vectors (Ad-CMV-Dest, Invitrogen) were constructed to express either E4-ORF3 (Ad-ORF3) or GFP (Ad-GFP).

**Plasmids, drugs and DNA damage.** pDONR221 plasmid for SUV39H1 was purchased from the Harvard Institute of Proteomics (Plasmid ID: HsCD00044660) and cloned into a CMV expression vector in frame with an N-terminal myc tag. Doxorubicin (dox, Sigma) at 0.5  $\mu$ M ml<sup>-1</sup> for 12 h was used as a positive control for p53 activation. 5-fluorouracil (Sigma) was used at 50  $\mu$ M ml<sup>-1</sup>, TSA (Sigma) at 5  $\mu$ M and nutlin-3 (Calbiochem) at 10  $\mu$ M.  $\gamma$  irradiation was performed via exposure to a cobalt-60 source.

**Protein lysates and western blot analysis.** Protein lysates were harvested, normalized and analysed as described previously<sup>21,22</sup>. Primary antibodies were from Santa Cruz Biotechnology (p53 DO-1 and FL393, GFP, MDM2 N20), Cell Signaling Technology (phospho-p53 serine (Ser) 6, 9, 15 (16G8), 20, 33, 46, 315, 392 and threonine (Thr) 81), Upstate (p21), Calbiochem (p53 Pab1620 and 240, MDM2 2A10), Abcam (actin and histone H3), Active Motif (H3K9), Ascension (E4-ORF3 (6A11)), ARF<sup>21</sup>, and E1B-55k (2A6). Actin expression was used as a loading control. Primary antibodies were detected with secondary antibodies labelled with either IRDye800 (Rockland), Alexa Fluor 680 (Molecular Probes) or horseradish peroxidase-conjugated secondary antibodies. Fluorescent antibodies were visualized using a LI-COR-Odyssey scanner and horseradish peroxidase antibodies with ECL chemiluminescence followed by autoradiography.

**RT-qPCR analysis.** RT-qPCR quantification of p53 transcriptional targets was performed using an ABI Prism 7900 system, as described previously<sup>21</sup>. Total RNA (1  $\mu$ g) was reverse-transcribed with Applied Biosystems' High Capacity Reverse Transcription. RT-qPCR reactions were set up using Taqman Fast mix (ABI), and run in triplicate. Input cDNA (10 ng) was used for 18S analysis, and 50 ng of input cDNA was used for all other targets. All samples were normalized to 18S expression.

**Immunofluorescence.** Cells were fixed in 4% paraformaldehyde and stained as described previously<sup>21,22</sup>. Primary antibodies were from Santa Cruz Biotechnology (p53 DO-1 and FL393, SUV39H2 Z-23), Cell Signaling Technology (SETDB1/ESET, G9a/EHMT2), Diagenode (H3K9me3 mouse), Active Motif (H3K9me3 rabbit), Abcam (SUV39H2, SUV39H1), and E1A (M73), Roche (myc 9E10), and Ascension (E4-ORF3 (6A11)). Alexa 488-, 555- and 633-conjugated secondary antibodies (Molecular Probes) were used for detection of primary antibodies. Images were acquired with a Zeiss Axioplan2 imaging system (Supplementary Figs 2a, 13, 17 and 20), a Nikon A1 laser confocal system (Figs 3d, e, 4b and Supplementary Figs 21, 25 and 26) and a Leica confocal SP2 (Supplementary Figs 18, 19 and 27). Pictures were edited in Adobe Photoshop. Background was corrected using same grey level values for all channels to remove noise, except for reducing the contrast of SETDB1 staining for the  $\Delta$ 55k/ $\Delta$ ORF3 panel in Supplementary Fig. 21. The raw microscope images acquired with the Nikon A1 laser confocal system were filtered with a 5 kernel median filter.

**Real-time luciferase assays.** U2OS cells were reverse-transfected with luciferase reporter plasmids, p53-luc, p53-mutant and pGL3 (Stratagene) using FuGENE 6 (Roche). After 36 h, cells were infected with viruses. After 4 h, medium was

replaced by high-glucose Dulbecco's modified Eagle's medium without phenol red, supplemented with 15 mM HEPES pH 7-7.4 (Gibco) and 100  $\mu$ M D-luciferin (BIOSYNTH Chemistry & Biology). Plates were sealed with vacuum grease (Dow Corning) and custom-made glass cover slips. Luciferase activity was analysed using the temperature-controlled Safire II plate reader with Magellan 6 software (Tecan Group). The luminescence for each well was integrated over 4 s and read at 1 h intervals for 48 h at a temperature setting of 37 °C. Data was graphed in Excel 2007 (Microsoft) by plotting the average luminescence of the triplicates at each time point.

**Chromatin immunoprecipitation assays.** p53 and H3K9me3 chromatin immunoprecipitations (ChIPs) were performed as described previously<sup>25,49</sup>. Cells were fixed with 1% formaldehyde for 15 min and stopped with 0.125 M glycine, lysed in Szak's modified RIPA buffer or 1% SDS lysis buffer and sonicated to shear genomic DNA. p53 and H3K9me3 ChIPs were performed using 2  $\mu$ g of p53 DO-1 monoclonal antibody and 5  $\mu$ l of anti-H3K9me3 rabbit serum (Active Motif), respectively. A mouse IgG isotype control and non-immune rabbit serum were used as controls for specificity. Immuno-complexes were isolated using Protein G (mouse antibodies) or Protein A beads (rabbit antibodies). Crosslinking was reversed by incubating at 65 °C overnight. DNA was purified and analysed using either semiquantitative PCR or RT-qPCR using conditions and primers described previously<sup>25,50,51</sup>. For RT-qPCR, samples were analysed in duplicate using a Sybr GreenER mix (Invitrogen) and quantified on a MyiQ RT-qPCR machine (Bio-Rad). A tenfold dilution series of input DNA was used to determine the efficiency of the PCR for each primer set. ChIP DNA samples were normalized relative to their respective input DNAs.

**Affymetrix expression arrays and data analysis.** Human primary quiescent SAECs were infected and harvested at 36 h.p.i. All samples were done in duplicate, and corresponding lysates were western-blotted. Total RNA was isolated and purified using TRIzol with the PureLink RNA Mini kit (Invitrogen), and treated with DNase I (Ambion). Total RNA (100 ng), spiked with Poly-A controls, was used to synthesize cDNA, according to recommended protocols using the Ambion WT Expression kit. Fragmentation and labelling of cDNA was performed as per the Affymetrix GeneChip WT Terminal Labeling standard protocol. Samples were hybridized to Affymetrix Human Exon 1.0ST arrays, washed, stained and scanned with the Affymetrix GCS 3000 7G and GeneChip Operating Software v1.3 to produce .CEL intensity files. Quality control analysis of all chips was performed with the Affymetrix expression console.

All array data were analysed using tools in the Partek Genomic Suite of software (Partek)<sup>52</sup>. Exon-level data were imported and filtered to include only those probes that are in the 'Core Meta-probeset', which represents 17,800 RefSeq genes and full-length GenBank mRNAs. A pre-background adjustment was performed for GC content followed by robust multi-array analysis (RMA) background correction, quantile normalization and mean probeset summarization<sup>53,54</sup> (Supplementary Fig. 29). Sources of variation due to random experimental factors, such as scan date and experiment were batch-removed using analysis of variance (ANOVA). The fold-change and *p*-values for differentially expressed genes between  $\Delta$ 55k/ $\Delta$ ORF3 versus mock,  $\Delta$ 55k versus mock,  $\Delta$ 55k/ $\Delta$ ORF3 versus  $\Delta$ 55k and nutlin versus mock were determined using linear contrasts in a one-way ANOVA model using method of moments<sup>52</sup>. The ANOVA model used was:

$$Y_{ij} = \mu + \text{virus/treatment}_i + \varepsilon_{ij}$$

where  $Y_{ij}$  represents the *j*th observation on the *i*th virus/treatment,  $\mu$  is the common effect for the whole experiment and  $\varepsilon_{ij}$  represents the random error present in the *j*th observation on the *i*th virus/treatment. The errors  $\varepsilon_{ij}$  are assumed to be normally and independently distributed with mean 0 and standard deviation  $\sigma$  for all measurements. A step-up false discovery rate (FDR) of 0.05 was applied to *p*-values calculated by ANOVA as the cut-off for significant differentially expressed genes.

Differentially expressed genes were analysed using the Genomatrix Pathway System (GePS) and GeneRanker programs, which uses information extracted from public and proprietary databases. Over-representation of different biological terms (Gene Ontology categories, signal transduction pathways) within the input gene list are calculated and listed together with their respective *p*-value<sup>55</sup>. Signal Transduction Pathway Associations are obtained by Genomatrix with a proprietary literature data mining algorithm based on all available Pubmed abstracts.

**Promoter analysis.** Genomatrix Gene2Promoter was used to retrieve the optimized promoters of the 265 differentially upregulated transcripts in  $\Delta$ 55k/ $\Delta$ ORF3- versus  $\Delta$ 55k-infected SAECs and filter them for p53 transcription factor binding sites (TFBS) using MatInspector<sup>56</sup>. MatInspector searches transcription factor matrix matches based on position weight matrices<sup>57</sup>, which has been used successfully to detect functional p53 transcription factor elements<sup>58</sup>. Six different matrices for p53 were used as described in Supplementary Table 4. Default

matrix indices (core similarity: 0.75; matrix similarity: optimized) were set during TFBS searching. The “core sequence” of a matrix is defined as the (usually 4) consecutive highest conserved positions of the matrix. The maximum core similarity of 1.0 is only reached when the highest conserved bases of a matrix match exactly in the sequence. The matrix similarity score takes into account all bases over the whole matrix length. A perfect match gets a score of 1.00, a “good” match to the matrix usually has a similarity of >0.80.

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